```
=> fil reg; d ide
FILE 'REGISTRY' ENTERED AT 09:33:42 ON 29 MAR 2007
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STRUCTURE FILE UPDATES:   28 MAR 2007  HIGHEST RN 928615-67-2
DICTIONARY FILE UPDATES:  28 MAR 2007  HIGHEST RN 928615-67-2

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TSCA INFORMATION NOW CURRENT THROUGH December 2, 2006

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REGISTRY includes numerically searchable data for experimental and
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http://www.cas.org/ONLINE/UG/regprops.html


L2    ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2007 ACS on STN
RN    83-88-5  REGISTRY
ED    Entered STN:  16 Nov 1984
CN    Riboflavin (8CI, 9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN    Benzo[g]pteridine, riboflavin deriv.
CN    Riboflavine (7CI)
OTHER NAMES:
CN    (-)-Riboflavin
CN    1-Deoxy-1-(3,4-dihydro-7,8-dimethyl-2,4-dioxobenzo[g]pteridin-10(2H)-yl)-D-
      ribitol
CN    6,7-Dimethyl-9-D-ribitylisoalloxazine
CN    6,7-Dimethyl-9-ribitylisoalloxazine
CN    Beflavin
CN    Beflavine
CN    Benzo[g]pteridine-2,4(3H,10H)-dione, 7,8-dimethyl-10-(D-ribo-2,3,4,5-
      tetrahydroxypentyl)-
CN    C.I. 50900
CN    C.I. Food Yellow 15
CN    D-Ribitol, 1-deoxy-1-(3,4-dihydro-7,8-dimethyl-2,4-dioxobenzo[g]pteridin-
      10(2H)-yl)-
CN    E 101
CN    E 101 (dye)
CN    Flavaxin
CN    Flavin BB
CN    Flaxain
CN    Food Yellow 15
CN    Hyre
CN    Lactobene
CN    Lactoflavin
CN    Lactoflavine
```
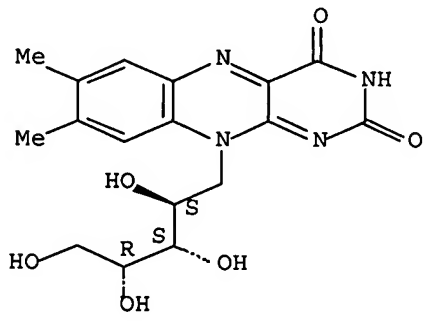

CN NCI 0033298
CN NSC 33298
CN Ribipca
CN Ribocrisina
CN Riboderm
CN Ribosyn
CN Ribotone
CN Ribovel
CN Russupteridine yellow III
CN San Yellow B
CN Vitaflavine
CN Vitamin B2
CN Vitamin G
CN Vitasan B2
FS STEREOSEARCH
DR 130609-39-1, 535950-32-4
MF C17 H20 N4 O6
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DRUGU, EMBASE, GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, PIRA, PROMT, PS, RTECS*, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

19703 REFERENCES IN FILE CA (1907 TO DATE)
322 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
19773 REFERENCES IN FILE CAPLUS (1907 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

INVENTOR SEARCH
=>
=> => fil medline drugb agricola pascal frosti caba biotechno biosis biotechds esbio lifesci fsta toxcenter bioeng ceaba embase dpci scisearch
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```
=> d que l95

L2            1 SEA FILE=REGISTRY ABB=ON  RIBOFLAVIN/CN
L84        1515 SEA FRANKE D?/AU
L85        3683 SEA HILL F?/AU
L86       32495 SEA MARTIN C?/AU
L87          22 SEA KNEBEL T?/AU
L88       26733 SEA L2
L89       51821 SEA RIBOFLAVIN OR RIBO FLAVIN OR VITAMIN B2 OR VITAMINB2
L90       33382 SEA MODIF?(2A)(B OR C OR BC)
L91       77692 SEA FLUIDI?(W) BED#
L92      674348 SEA PRECIPITAT?
L93       25900 SEA (ACID#(2A)(MINERAL OR INORG?))
L94     1406599 SEA GRANUL?
L95           5 SEA (L84 AND L85 AND L86 AND L87) OR ((L84 OR L85 OR L86 OR
                L87) AND (L88 OR L89) AND (L90 OR L91 OR L92 OR L93 OR L94))


=> fil wpix; d que l43

FILE 'WPIX' ENTERED AT 10:28:29 ON 29 MAR 2007
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FILE LAST UPDATED:                          22 MAR 2007   <20070322/UP>
MOST RECENT THOMSON SCIENTIFIC UPDATE:     200720      <200720/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> New reloaded DWPI Learn File (LWPI) available as well <<<

>>> YOU ARE IN THE NEW AND ENHANCED DERWENT WORLD PATENTS INDEX <<<

>>> New display format FRAGHITSTR available <<<
    SEE ONLINE NEWS and
http://www.stn-international.de/archive/stn_online_news/fraghitstr_ex.pdf

>>> IPC Reform backfile reclassification has been loaded to 31 December
    2006. No update date (UP) has been created for the reclassified
    documents, but they can be identified by 20060101/UPIC and
    20061231/UPIC. <<<

FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
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http://www.stn-international.de/training_center/patents/stn_guide.pdf

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http://www.stn-international.de/stndatabases/details/ipc_reform.html and
http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf


>>> FOR DETAILS ON THE NEW AND ENHANCED DERWENT WORLD PATENTS INDEX
    PLEASE SEE
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<
'BI ABEX' IS DEFAULT SEARCH FIELD FOR 'WPIX' FILE


L27          79 SEA FILE=WPIX ABB=ON  FRANKE D?/AU
L28         156 SEA FILE=WPIX ABB=ON  HILL F?/AU
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L29          787 SEA FILE=WPIX ABB=ON  MARTIN C?/AU
L30            5 SEA FILE=WPIX ABB=ON  KNEBEL T?/AU
L31         3154 SEA FILE=WPIX ABB=ON  RIBOFLAVIN#/BI,ABEX OR RIBO FLAVIN#/BI,AB
               EX OR VITAMIN B2/BI,ABEX
L32       153807 SEA FILE=WPIX ABB=ON  GRANUL?/BI,ABEX
L33         6414 SEA FILE=WPIX ABB=ON  FLUIDIZED BED#/BI,ABEX
L34       139368 SEA FILE=WPIX ABB=ON  PRECIPITAT?/BI,ABEX
L35        32098 SEA FILE=WPIX ABB=ON  ACID#/BI,ABEX(2A)(MINERAL/BI,ABEX OR
               INORG?/BI,ABEX)
L36       323133 SEA FILE=WPIX ABB=ON  MODIF?/BI,ABEX
L40            2 SEA FILE=WPIX ABB=ON  (RIBOFLAVIN/CN OR "RIBOFLAVIN HYDROCHLORI
               DE"/CN)
L41         1923 SEA FILE=WPIX ABB=ON  L40/DCR
L42         1924 SEA FILE=WPIX ABB=ON  (0503/DRN,DCN,DCRE OR R00503/DRN,DCN,DCRE
                OR R16015/DRN,DCN,DCRE OR R18174/DRN,DCN,DCRE OR 105627-0-0-0/
               DRN,DCN,DCRE OR 105627-0-1-0/DRN,DCN,DCRE)
L43            4 SEA FILE=WPIX ABB=ON  (L27 OR L28 OR L29 OR L30) AND (L31 OR
               L41 OR L42) AND (L32 OR L33 OR L34 OR L35 OR L36)


=> fil uspatf; d que l71

FILE 'USPATFULL' ENTERED AT 10:28:31 ON 29 MAR 2007
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 27 Mar 2007 (20070327/PD)
FILE LAST UPDATED: 27 Mar 2007 (20070327/ED)
HIGHEST GRANTED PATENT NUMBER: US7197769
HIGHEST APPLICATION PUBLICATION NUMBER: US2007067883
CA INDEXING IS CURRENT THROUGH 27 Mar 2007 (20070327/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 27 Mar 2007 (20070327/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Oct 2006
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Oct 2006


L2             1 SEA FILE=REGISTRY ABB=ON  RIBOFLAVIN/CN
L58         1373 SEA FILE=USPATFULL ABB=ON  L2
L59        42967 SEA FILE=USPATFULL ABB=ON  MODIF?(2A)(B OR C OR BC)
L60          306 SEA FILE=USPATFULL ABB=ON  (MODIF?(2A)(B OR C OR BC))/IT
L62           41 SEA FILE=USPATFULL ABB=ON  FRANKE D?/AU
L63          156 SEA FILE=USPATFULL ABB=ON  HILL F?/AU
L64          650 SEA FILE=USPATFULL ABB=ON  MARTIN C?/AU
L65            1 SEA FILE=USPATFULL ABB=ON  KNEBEL T?/AU
L66         9695 SEA FILE=USPATFULL ABB=ON  RIBOFLAVIN# OR RIBO FLAVIN# OR
               VITAMIN B2
L67         1387 SEA FILE=USPATFULL ABB=ON  (RIBOFLAVIN# OR RIBO FLAVIN# OR
               VITAMIN B2)/IT
L69       274514 SEA FILE=USPATFULL ABB=ON  GRANUL?
L70         9334 SEA FILE=USPATFULL ABB=ON  GRANUL?/IT
L71            4 SEA FILE=USPATFULL ABB=ON  (L62 OR L63 OR L64 OR L65) AND (L58
               OR L66 OR L67) AND (L59 OR L60 OR L69 OR L70)


=> fil capl; d que l1; d que l7; d que l11

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FILE COVERS 1907 - 29 Mar 2007 VOL 146 ISS 14
FILE LAST UPDATED: 28 Mar 2007 (20070328/ED)

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http://www.cas.org/infopolicy.html
'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE

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L1             1 SEA FILE=CAPLUS ABB=ON  US2005-552137/AP



L3           191 SEA FILE=CAPLUS ABB=ON  FRANKE D?/AU
L4           583 SEA FILE=CAPLUS ABB=ON  HILL F?/AU
L5          4551 SEA FILE=CAPLUS ABB=ON  MARTIN C?/AU
L6             4 SEA FILE=CAPLUS ABB=ON  KNEBEL T?/AU
L7             1 SEA FILE=CAPLUS ABB=ON  L6 AND (L3 OR L4 OR L5)



L2             1 SEA FILE=REGISTRY ABB=ON  RIBOFLAVIN/CN
L3           191 SEA FILE=CAPLUS ABB=ON  FRANKE D?/AU
L4           583 SEA FILE=CAPLUS ABB=ON  HILL F?/AU
L5          4551 SEA FILE=CAPLUS ABB=ON  MARTIN C?/AU
L6             4 SEA FILE=CAPLUS ABB=ON  KNEBEL T?/AU
L8         19773 SEA FILE=CAPLUS ABB=ON  L2
L10       131793 SEA FILE=CAPLUS ABB=ON  GRANUL?/OBI
L11            3 SEA FILE=CAPLUS ABB=ON  (L3 OR L4 OR L5 OR L6) AND L8 AND L10


=> s l1,l7,l11

L102           3 (L1 OR L7 OR L11)

=> dup rem l102,l95,l43,l71

DUPLICATE IS NOT AVAILABLE IN 'DPCI'.
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PROCESSING COMPLETED FOR L102
PROCESSING COMPLETED FOR L95
PROCESSING COMPLETED FOR L43
PROCESSING COMPLETED FOR L71
L103          15 DUP REM L102 L95 L43 L71 (1 DUPLICATE REMOVED)
                 ANSWERS '1-3' FROM FILE CAPLUS
                 ANSWER '4' FROM FILE LIFESCI
                 ANSWER '5' FROM FILE BIOENG
                 ANSWERS '6-8' FROM FILE DPCI
                 ANSWERS '9-11' FROM FILE WPIX
                 ANSWERS '12-15' FROM FILE USPATFULL

=> d abs ibib hitstr 1-3; d iall 4-8; d iall abeq tech 9-11; d ibib abs hitind 12-
15

L103 ANSWER 1 OF 15  CAPLUS  COPYRIGHT 2007 ACS on STN DUPLICATE 1
AB    Free-flowing, non-dusting, binder-free, granular riboflavin (I) is prepared
      by, e.g., processing aqueous or aqueous containing suspensions of pure finely
      divided I in a spray fluidized-bed dryer.
ACCESSION NUMBER:         1992:21414  CAPLUS  Full-text
DOCUMENT NUMBER:          116:21414
TITLE:                    Preparation of granular riboflavin with
                          improved workability
INVENTOR(S):              Grimmer, Johannes; Kiefer, Hans; Martin,
                          Christoph
PATENT ASSIGNEE(S):       BASF A.-G., Germany
SOURCE:                   Ger. Offen., 5 pp.
                          CODEN: GWXXBX
DOCUMENT TYPE:            Patent
LANGUAGE:                 German
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
     ---------------      ----   --------    --------------------     --------
     DE 4014262            A1    19911107    DE 1990-4014262          19900504
     JP 04224515           A     19920813    JP 1991-86472            19910418
     JP 2536973            B2    19960925
     CA 2040862            A1    19911105    CA 1991-2040862          19910419
     EP 457075             A2    19911121    EP 1991-106676           19910425
     EP 457075             A3    19920701
     EP 457075             B1    19960207
        R:  CH, DE, DK, FR, GB, IT, LI, NL
     US 5300303            A     19940405    US 1992-920539           19920728
PRIORITY APPLN. INFO.:                       DE 1990-4014262      A   19900504
                                             US 1991-692854       B1  19910429
IT    83-88-5P, Riboflavin, preparation
      RL: SPN (Synthetic preparation); PREP (Preparation)
         (preparation of, with improved workability properties, method for)
```
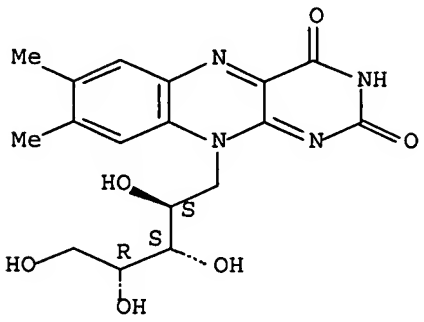

RN 83-88-5 CAPLUS
CN Riboflavin (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 2 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
AB The present invention concerns an improved procedure for the production of pure riboflavin (vitamin B2) of the modification B/C in granular form. Beyond that the invention concerns pure riboflavin in granular form of bulk d. 0.45-0.7 g/mL and, after tabletting, release kinetics (dissoln.) of ≥ 80%.

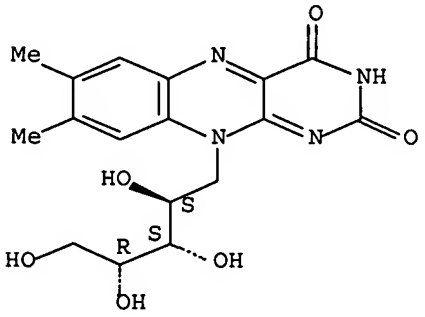
ACCESSION NUMBER: 2004:870938 CAPLUS Full-text
DOCUMENT NUMBER: 141:349140
TITLE: Procedure for the production of riboflavin of the modification B/C in **granular** form.
INVENTOR(S): **Franke, Dirk; Hill, Friedrich; Martin, Christoph; Knebel, Thomas**
PATENT ASSIGNEE(S): BASF A.-G., Germany
SOURCE: Ger. Offen., 9 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10317051	A1	20041021	DE 2003-10317051	20030411
CA 2521633	A1	20041021	CA 2004-2521633	20040407
WO 2004089889	A2	20041021	WO 2004-EP3689	20040407
WO 2004089889	A3	20050602		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1615927	A2	20060118	EP 2004-726106	20040407
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
CN 1774438	A	20060517	CN 2004-80009764	20040407

JP 2006522763	T	20061005	JP 2006-505032		20040407
US 2006258664	A1	20061116	US 2005-552137		20051006 <--
PRIORITY APPLN. INFO.:			DE 2003-10317051	A	20030411
			WO 2004-EP3689	W	20040407

IT **83-88-5P**, Riboflavin, biological studies
RL: FFD (Food or feed use); IMF (Industrial manufacture); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); USES (Uses)
(procedure for the production of riboflavin of the modification B/C in **granular** form.)
RN 83-88-5 CAPLUS
CN Riboflavin (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 3 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
AB Riboflavin in the form of a dry powder is produced by drying the discharge from a riboflavin fermentation in a fluidized-bed dryer. Thus, an aqueous suspension, concentrated from a fermentor discharge containing 19.7% solids (24% of which was riboflavin) was continuously sprayed onto a fluidized bed at 20° along with a fluidizing gas at 140-150°. The input was mixed so that the bed temperature was 75°. A part of the fluidized-bed receiver was continuously withdrawn and separated into 3 fractions by particle size. Only 4% of the product had a particle size >250 μm, while 50% had a particle size of 100-250 μm and 45% had a particle size of <100 μm.

ACCESSION NUMBER:	1990:215214 CAPLUS Full-text
DOCUMENT NUMBER:	112:215214
TITLE:	**Granulation** of microbially produced riboflavin
INVENTOR(S):	Meyer, Joachim; Buehler, Wolfgang; Grimmer, Johannes; Eipper, Gunter; Kiefer, Hans; **Martin, Christoph**
PATENT ASSIGNEE(S):	BASF A.-G., Fed. Rep. Ger.
SOURCE:	Ger. Offen., 5 pp. CODEN: GWXXBX
DOCUMENT TYPE:	Patent
LANGUAGE:	German
FAMILY ACC. NUM. COUNT:	1

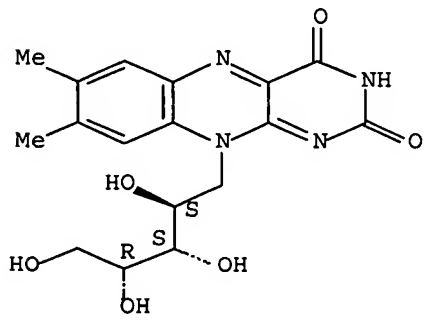
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 3819745	A1	19891214	DE 1988-3819745	19880610
EP 345717	A2	19891213	EP 1989-110187	19890606
EP 345717	A3	19910116		

EP 345717	B1	19930512			
R: BE, CH, DE, ES, FR, GB, IT, LI, NL					
ES 2040932	T3	19931101	ES 1989-110187		19890606
CA 1329361	C	19940510	CA 1989-601910		19890606
DK 8902817	A	19891211	DK 1989-2817		19890609
DK 174850	B1	20031222			
JP 02057188	A	19900226	JP 1989-145546		19890609
JP 08029109	B	19960327			
US 4977190	A	19901211	US 1989-363853		19890609
CN 1038751	A	19900117	CN 1989-103885		19890610
CN 1015596	B	19920226			
PRIORITY APPLN. INFO.:			DE 1988-3819745	A	19880610

IT **83-88-5P**, Riboflavin, preparation
RL: PREP (Preparation)
(manufacture of **granulated**, by drying of fermentation broth)
RN 83-88-5 CAPLUS
CN Riboflavin (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



L103 ANSWER 4 OF 15 LIFESCI COPYRIGHT 2007 CSA on STN
ACCESSION NUMBER: 90:63698 LIFESCI Full-text
TITLE: Preparation of **riboflavin**, produced by a microbial method, in the form of spray-dried **granules** or microgranules.
AUTHOR: Meyer, J.; Buehler, W.; Grimmer, J.; Eipper, G.; Kiefer, H.; **Martin, C.**
CORPORATE SOURCE: BASF Aktiengesellschaft, Lundwigshafen (FRG)
PATENT INFO.: US 4977190 1990
SOURCE: (1990) . US Cl. 514/951; Int. Cl. C07D 471/00..
DOCUMENT TYPE: Patent
FILE SEGMENT: A
LANGUAGE: English
CLASSIFICATION: 01006 Enzymes & cofactors
UNCONTROLLED TERM: microorganisms; fermentation; riboflavine; patents; production

L103 ANSWER 5 OF 15 BIOENG COPYRIGHT 2007 CSA on STN
ACCESSION NUMBER: 2004192150 BIOENG Full-text
DOCUMENT NUMBER: 2421487
TITLES: Preparation of **riboflavin**, produced by a microbial method, in the form of spray-dried

granules or microgranules.
AUTHOR: Meyer, J; Buehler, W; Grimmer, J; Eipper, G; Kiefer, H; Martin, C
CORPORATE SOURCE: BASF Aktiengesellschaft, Lundwigshafen (FRG)
SOURCE: US Patent 4,977,190, , 1990
NUMBER OF REPORT: US Patent 4,977,190
DOCUMENT TYPE: Patent
LANGUAGE: English
NOTE: US Cl. 514/951; Int. Cl. C07D 471/00.
OTHER SOURCE: Microbiology Abstracts A: Industrial & Applied Microbiology
CLASSIFICATION CODE: 01006 Enzymes & cofactors
CONTROLLED TERMS: microorganisms; fermentation; riboflavine
UNCONTROLLED TERMS: patents; production

L103 ANSWER 6 OF 15 DPCI COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-748715 [73] DPCI
DOC. NO. CPI: C2004-263148
TITLE: Rapidly dissolving, high bulk density granular riboflavin in B/C modification, for food or pharmaceutical use, obtained by precipitation from aqueous mineral acid and fluidized bed spray granulation.
DERWENT CLASS: B02 D13
INVENTOR(S): FRANKE, D; HILL, F; KNEBEL, T ; MARTIN, C
PATENT ASSIGNEE(S): (BADI) BASF AG
COUNTRY COUNT: 109
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2004089889	A2	20041021	(200473)*	GE	15	C07D000-00
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW						
DE 10317051	A1	20041021	(200473)			C07D475-14
EP 1615927	A2	20060118	(200606)	GE		C07D475-00
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IT LI LT LU LV MC MK NL PL PT RO SE SI SK TR						
KR 2006006028	A	20060118	(200659)			A61K009-16
CN 1774438	A	20060517	(200663)			C07D475-00
JP 2006522763	W	20061005	(200667)		18	A61K031-519
US 2006258664	A1	20061116	(200677)			A61K031-519

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004089889	A2	WO 2004-EP3689	20040407
DE 10317051	A1	DE 2003-10317051	20030411
EP 1615927	A2	EP 2004-726106	20040407
		WO 2004-EP3689	20040407
KR 2006006028	A	WO 2004-EP3689	20040407
		KR 2005-719236	20051010

CN 1774438	A	CN 2004-Y9764	20040407
JP 2006522763	W	WO 2004-EP3689	20040407
		JP 2006-505032	20040407
US 2006258664	A1	WO 2004-EP3689	20040407
		US 2005-552137	20051006

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1615927	A2Based on	WO 2004089889
KR 2006006028	A Based on	WO 2004089889
JP 2006522763	W Based on	WO 2004089889

PRIORITY APPLN. INFO: DE 2003-10317051 20030411
INT. PATENT CLASSIF.:
MAIN: A61K009-16; A61K031-519; A61K031-525; C07D000-00; C07D475-00; C07D475-14
SECONDARY: A23L001-302; B01D009-00; B01D009-02; B01J002-00; B01J002-16; C07D475-02
FILE SEGMENT: CPI

EXF EXAMINER'S FIELD OF SEARCH UPE: 20060216

CTCS CITATION COUNTERS

PNC.DI	0	Cited Patents Count (by inventor)
PNC.DX	5	Cited Patents Count (by examiner)
IAC.DI	0	Cited Issuing Authority Count (by inventor)
IAC.DX	1	Cited Issuing Authority Count (by examiner)
PNC.GI	0	Citing Patents Count (by inventor)
PNC.GX	0	Citing Patents Count (by examiner)
IAC.GI	0	Citing Issuing Authority Count (by inventor)
IAC.GX	0	Citing Issuing Authority Count (by examiner)
CRC.I	0	Cited Literature References Count (by inventor)
CRC.X	1	Cited Literature References Count (by examiner)
OSC.D	5	Cited Patent WPI Accession Number Count
OSC.G	0	Citing Patent WPI Accession Number Count

CDP CITED PATENTS UPD: 20060216

Cited by Examiner

CITING PATENT	CAT	CITED PATENT	ACCNO
EP 1615927	A2	No Citations	
WO 2004089889	A2 AD	EP 307767	A 1989-087185/12
	PA:	(HOFF) HOFFMANN-LA ROCHE AG	
	IN:	**HERENA, L E; RAMANARAYA, K**	
	AD	EP 457075	A 1991-333665/46
	PA:	(BADI) BASF AG; (GRIM-I) GRIMMER J	
	IN:	**GRIMMER, J; KIEFER, H; MARTIN, C**	
	Y	EP 730034	A1 1996-395058/40

PA: (HOFF) HOFFMANN LA ROCHE & CO AG F
IN: **KUPFER, E**
YD EP 995749 A1 2000-294952/26
PA: (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) ROCHE VITAMINS INC
IN: **WAGNER, G**
YD EP 1048668 A2 2000-681202/67
PA: (HOFF) HOFFMANN LA ROCHE LTD F; (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) HOFFMANN LA ROCHE & CO KG F; (STAM) DSM IP ASSETS BV; (HOFF) ROCHE VITAMINS INC
IN: **NOWOTNY, M; TRITSCH, J**

REN LITERATURE CITATIONS UPR: 20060216

Citations by Examiner

CITING PATENT	CAT	CITED LITERATURE
EP 1615927	A2	See references of WO 2004089889A2

L103 ANSWER 7 OF 15 DPCI COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1991-333665 [46] DPCI
DOC. NO. NON-CPI: N1991-255662
DOC. NO. CPI: C1991-144003
TITLE: Free-flowing, non dusting **riboflavin granulate** - prepared by subjecting aqueous or water-containing **riboflavin** suspension to **fluidised bed** drying or to single nozzle plate atomising.
DERWENT CLASS: B02 D13 E13 Q76
INVENTOR(S): GRIMMER, J; KIEFER, H; **MARTIN, C**
PATENT ASSIGNEE(S): (BADI) BASF AG; (GRIM-I) GRIMMER J
COUNTRY COUNT: 11
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
DE 4014262	A	19911107	(199146)*			
EP 457075	A	19911121	(199147)			
R: CH DE FR GB IT LI						
CA 2040862	A	19911105	(199205)			
JP 04224515	A	19920813	(199239)		5	A61K031-525
EP 457075	A3	19920701	(199333)			
US 5300303	A	19940405	(199413)		4	A61K009-14
EP 457075	B1	19960207	(199610)	GE	7	C07D475-14
R: CH DE DK FR GB IT LI NL						
DE 59107371	G	19960321	(199617)			C07D475-14
JP 2536973	B2	19960925	(199643)		4	A61K031-525

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
DE 4014262	A	DE 1990-4014262	19900504
EP 457075	A	EP 1991-106676	19910425
JP 04224515	A	JP 1991-86472	19910418
EP 457075	A3	EP 1991-106676	19910425
US 5300303	A Cont of	US 1991-692854	19910429

		US 1992-920539	19920728
EP 457075	B1	EP 1991-106676	19910425
DE 59107371	G	DE 1991-507371	19910425
		EP 1991-106676	19910425
JP 2536973	B2	JP 1991-86472	19910418

FILING DETAILS:

PATENT NO	KIND	PATENT NO
DE 59107371	G Based on	EP 457075
JP 2536973	B2Previous Publ.	JP 04224515

PRIORITY APPLN. INFO: DE 1990-4014262 19900504
INT. PATENT CLASSIF.:
MAIN: A61K009-14; A61K031-525; C07D475-14
SECONDARY: A61K009-16; A61K031-52; B01J002-04; F26B003-08
FILE SEGMENT: CPI GMPI

CTCS CITATION COUNTERS

PNC.DI	0	Cited Patents Count (by inventor)
PNC.DX	12	Cited Patents Count (by examiner)
IAC.DI	0	Cited Issuing Authority Count (by inventor)
IAC.DX	3	Cited Issuing Authority Count (by examiner)
PNC.GI	0	Citing Patents Count (by inventor)
PNC.GX	12	Citing Patents Count (by examiner)
IAC.GI	0	Citing Issuing Authority Count (by inventor)
IAC.GX	4	Citing Issuing Authority Count (by examiner)
CRC.I	0	Cited Literature References Count (by inventor)
CRC.X	0	Cited Literature References Count (by examiner)
OSC.D	8	Cited Patent WPI Accession Number Count
OSC.G	8	Citing Patent WPI Accession Number Count

CDP CITED PATENTS UPD: 19961125

Cited by Examiner

CITING PATENT	CAT	CITED PATENT	ACCNO
EP 457075	A	No Citations	
EP 457075	A3	EP 219276	1987-110206/16
	PA:	(TAKE) TAKEDA CHEM IND LTD	
	IN:	IZUHARA, S; KITAMORI, N; MAENO, M	
		EP 307767	1989-087185/12
	PA:	(HOFF) HOFFMANN-LA ROCHE AG	
	IN:	HERENA, L E; RAMANARAYA, K	
		EP 345717	1989-365498/50
	PA:	(BADI) BASF AG	
	IN:	BUEHLER, W; EIPPER, G; GRIMMER, J; KIEFER, H; MARTIN, C; MEYER, J	
		EP 414115	1991-059372/09
	PA:	(BADI) BASF AG	
	IN:	BUEHLER, V; PETERSEN, H	
		US 4994458 A	1991-072935/10

PA: (BADI) BASF CORP
IN: KILBRIDE, T K
US 5000888 A 1991-101430/14
PA: (BADI) BASF CORP
IN: KILBRIDE, T K; LISA, R E
EP 457075 B1 EP 219276 A 1987-110206/16
PA: (TAKE) TAKEDA CHEM IND LTD
IN: IZUHARA, S; KITAMORI, N; MAENO, M
EP 307767 A 1989-087185/12
PA: (HOFF) HOFFMANN-LA ROCHE AG
IN: HERENA, L E; RAMANARAYA, K
EP 345717 A 1989-365498/50
PA: (BADI) BASF AG
IN: BUEHLER, W; EIPPER, G; GRIMMER, J; KIEFER, H; MARTIN, C; MEYER, J
EP 414115 A 1991-059372/09
PA: (BADI) BASF AG
IN: BUEHLER, V; PETERSEN, H
US 4994458 A 1991-072935/10
PA: (BADI) BASF CORP
IN: KILBRIDE, T K
US 5000888 A 1991-101430/14
PA: (BADI) BASF CORP
IN: KILBRIDE, T K; LISA, R E
JP 2536973 B2 JP 58144385 A 1983-779952/40
PA: (KAWA-I) KAWASHIMA Y
JP 59120235 A 1984-159175/26
PA: (FARB) BAYER AG
IN: HAUSMANN, H; NEUMAIER, H

CGP CITING PATENTS UPG: 20050816

Cited by Examiner

CITED PATENT	CAT	CITING PATENT	ACCNO
DE 4014262	A	DE 4206752	C2 1993-289144/37
	PA:	(SUDD) SKW TROSTBERG AG	
	IN:	KNIEP, P; ZAHN, K	
		US 6440462	B1 1997-479856/41
	PA:	(BIOC) BIOCHEMIE GMBH	
	IN:	RANEBURGER, J; ZEISL, E; ZIESL, E	
DE 4014262	A1	US 6150364	A 2000-294952/22
	PA:	(HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) ROCHE VITAMINS INC	
	IN:	WAGNER, G	
EP 457075	A YD	EP 1048668	A 2000-681202/62
	PA:	(HOFF) HOFFMANN LA ROCHE LTD F; (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) HOFFMANN LA ROCHE & CO KG F	
	IN:	NOWOTNY, M; TRITSCH, J	
		EP 1048668	B1 2000-681202/62
	PA:	(HOFF) HOFFMANN LA ROCHE LTD F; (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) HOFFMANN LA ROCHE & CO KG F	
	IN:	NOWOTNY, M; TRITSCH, J	
	A	EP 1075830	A 2001-193193/22
	PA:	(ABOC-N) ABOCA DI MERCATI & C SNC VALENTINO	
	IN:	VALENTINO, M; MERCATI, V	
		EP 1075830	B1 2001-193193/22

PA: (ABOC-N) ABOCA DI MERCATI & C SNC VALENTINO; (ABOC-N) ABOCA SPA
IN: VALENTINO, M; MERCATI, V
US 6207189 B1 2001-193193/22
PA: (ABOC-N) ABOCA DI MERCATI & C SNC VALENTINO
IN: VALENTINO, M; MERCATI, V
US 6468580 B1 2001-104913/12
PA: (BADI) BASF AG
IN: CHOI, J S; DU, Y S; EIDELSBURGER, U; KIM, S H; KIM, T H; MEYER, J
US 6723346 B1 2000-681202/62
PA: (HOFF) HOFFMANN LA ROCHE LTD F; (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) HOFFMANN LA ROCHE & CO KG F; (HOFF) ROCHE VITAMINS INC
IN: NOWOTNY, M; TRITSCH, J
AD WO 2004089889 A2 2004-748715/72
PA: (BADI) BASF AG
IN: FRANKE, D; HILL, F; KNEBEL, T; MARTIN, C
US 5300303 A YD EP 1048668 A 2000-681202/62
PA: (HOFF) HOFFMANN LA ROCHE LTD F; (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) HOFFMANN LA ROCHE & CO KG F
IN: NOWOTNY, M; TRITSCH, J
EP 1048668 B1 2000-681202/62
PA: (HOFF) HOFFMANN LA ROCHE LTD F; (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) HOFFMANN LA ROCHE & CO KG F
IN: NOWOTNY, M; TRITSCH, J
US 6093715 A 2000-514118/42
PA: (BADI) BASF AG
IN: HARZ, H; SCHMIDT, D N; SCHWEIKERT, L
US 6150364 A 2000-294952/22
PA: (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) ROCHE VITAMINS INC
IN: WAGNER, G
US 6440462 B1 1997-479856/41
PA: (BIOC) BIOCHEMIE GMBH
IN: RANEBURGER, J; ZEISL, E; ZIESL, E
US 6723346 B1 2000-681202/62
PA: (HOFF) HOFFMANN LA ROCHE LTD F; (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) HOFFMANN LA ROCHE & CO KG F; (HOFF) ROCHE VITAMINS INC
IN: NOWOTNY, M; TRITSCH, J

L103 ANSWER 8 OF 15 DPCI COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1989-365498 [50] DPCI
DOC. NO. CPI: C1989-162022
TITLE: Production of **riboflavin**-containing feed additive **granules** - from fermentation broth by **fluidised bed** or atomisation drying without addition of binder.
DERWENT CLASS: B02 C02 D13 D16 E13
INVENTOR(S): BUEHLER, W; EIPPER, G; GRIMMER, J; KIEFER, H; **MARTIN**, C; MEYER, J
PATENT ASSIGNEE(S): (BADI) BASF AG
COUNTRY COUNT: 14
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
EP 345717	A	19891213	(198950)*	GE	8	
R: BE CH DE ES FR GB IT LI NL						

DE 3819745	A	19891214	(198951)		
DK 8902817	A	19891211	(199010)		
JP 02057188	A	19900226	(199014)		
CN 1038751	A	19900117	(199043)		
US 4977190	A	19901211	(199101)		
EP 345717	B1	19930512	(199319)	GE	9 A23K001-16
R: BE CH DE ES FR GB IT LI NL					
DE 58904314	G	19930617	(199325)		A23K001-16
ES 2040932	T3	19931101	(199348)		A23K001-16
CA 1329361	C	19940510	(199424)		C12P025-00
JP 08029109	B2	19960327	(199617)		4 C12P017-18
DK 174850	B	20031222	(200407)		B01J002-16

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 345717	A	EP 1989-110187	19890606
DE 3819745	A	DE 1988-3819745	19880610
JP 02057188	A	JP 1989-145546	19890609
US 4977190	A	US 1989-363853	19890609
EP 345717	B1	EP 1989-110187	19890606
DE 58904314	G	DE 1989-504314	19890606
		EP 1989-110187	19890606
ES 2040932	T3	EP 1989-110187	19890606
CA 1329361	C	CA 1989-601910	19890606
JP 08029109	B2	JP 1989-145546	19890609
DK 174850	B	DK 1989-2817	19890609

FILING DETAILS:

PATENT NO	KIND	PATENT NO
DE 58904314	G Based on	EP 345717
ES 2040932	T3Based on	EP 345717
JP 08029109	B2Previous Publ.	JP 02057188
DK 174850	B Previous Publ.	DK 8902817

PRIORITY APPLN. INFO: DE 1988-3819745 19880610
INT. PATENT CLASSIF.: A23K001-16; A23P001-02; A61K009-14; B01J002-04;
C07D471-00; C07D475-02; C07D487-04; C12P017-10;
C12P017-18; C12P025-00
MAIN: B01J002-16; C12P017-18; C12P025-00
SECONDARY: A23P001-02; A61K009-14; A61K031-525; B01J002-04;
C07D471-00; C07D475-02; C07D475-14; C07D487-04;
C12P017-10
ADDITIONAL: A23K001-16
INDEX: C07D475:02
FILE SEGMENT: CPI

CTCS CITATION COUNTERS

PNC.DI	0	Cited Patents Count (by inventor)
PNC.DX	12	Cited Patents Count (by examiner)
IAC.DI	0	Cited Issuing Authority Count (by inventor)
IAC.DX	5	Cited Issuing Authority Count (by examiner)
PNC.GI	0	Citing Patents Count (by inventor)
PNC.GX	14	Citing Patents Count (by examiner)
IAC.GI	0	Citing Issuing Authority Count (by inventor)

IAC.GX 2 Citing Issuing Authority Count (by examiner)

CRC.I 0 Cited Literature References Count (by inventor)
CRC.X 1 Cited Literature References Count (by examiner)

OSC.D 12 Cited Patent WPI Accession Number Count
OSC.G 6 Citing Patent WPI Accession Number Count

CDP CITED PATENTS UPD: 19951031

Cited by Examiner

CITING PATENT	CAT	CITED PATENT	ACCNO
EP 345717	A	EP 198431	A 1986-280129/43
	PA:	(BADI) BASF CORP; (BADI) BASF AG	
	IN:	FINNAN, J L; LISA, R E; WISNIACH, J T	
		GB 1226799	A 1970-56906R/32
	PA:	(GOR -N) INSTITUT GORVUCHIKH ISKOP	
		SU 652422	A 1979-87290B/48
	PA:	(HEAT-R) HEAT MASS EXCHANGE	
	IN:	BOGDANOV, V M; BRUSINENKO, V I; ZEDLETS, I I	
		SU 807009	A 1981-86919D/47
	PA:	(KIPO) KIEV POLY	
	IN:	BARABASH, P A; KURILOVA, E B; MUZHILKO, A A	
		SU 840628	A 1982-32680E/16
	PA:	(KIPO) KIEV POLY	
	IN:	BARABASH, P A; MUZHILKO, A A; RIFERT, V G	
EP 345717	B1	EP 198431	A 1986-280129/43
	PA:	(BADI) BASF CORP; (BADI) BASF AG	
	IN:	FINNAN, J L; LISA, R E; WISNIACH, J T	
		GB 1226799	A 1970-56906R/32
	PA:	(GOR -N) INSTITUT GORVUCHIKH ISKOP	
		SU 652422	A 1979-87290B/48
	PA:	(HEAT-R) HEAT MASS EXCHANGE	
	IN:	BOGDANOV, V M; BRUSINENKO, V I; ZEDLETS, I I	
US 4977190	A	DE 2920592	1979-66229B/36
	PA:	(MERI) MERCK & CO INC	
	IN:	EPSTEIN, A; GRAHAM, G; SKLARZ, W A	
		DE 3344509	1984-153682/25
	PA:	(BADI) BASF AG	
	IN:	BEYSE, H J; EIPPER, G; HOFMANN, F; LANGENFELD, H	
		DE 3420310	1985-020681/04
	PA:	(GENE-R) GENETICS & IND MICR; (VNII-R) VNIIGENETIKA	
	IN:	GALUSHKINA, Z M; KHAIKINSON, M Y; KUKANOVA, A Y; LOMANTAS, Y A V; RABINOVICH, P M; STEPANOV, A I; ZHDANOV, V G	
		EP 121877	A 1984-257414/42
	PA:	(BADI) BASF AG	
	IN:	BEYSE, H J; EIPPER, G; LANGENFELD, H	
		EP 211289	1987-051528/08
	PA:	(DAIL) DAICEL CHEM IND LTD	
	IN:	KAGEYAMA, S; KAWAI, K; MATSUYAMA, A; TAKAO, S	
		EP 231605	1987-222707/32
	PA:	(COOA) COORS CO ADOLPH; (ZEAG-N) ZEAGEN INC	
	IN:	BOYTS, A; BURDZINSKI, L; HEEFNER, D L; YARUS, M; BURDZINSKI, L A; WEAVER, C A; YARUS, M J	
		US 3959472	A 1973-66559U/44

PA: (HOFF) HOFFMANN-LA ROCHE AND CO

REN LITERATURE CITATIONS UPR: 19951031

Citations by Examiner

CITING PATENT	CAT	CITED LITERATURE
US 4977190	A	Kroll, Trocknungstechnik, BD. II: "Trockner und Trocknungsverfahren", 2. Ed., Springer Verlag, Berlin 1978, pp. 221-224.

CGP CITING PATENTS UPG: 20061001

Cited by Examiner

CITED PATENT	CAT	CITING PATENT	ACCNO
DE 3819745		US 4994458	A 1991-072935/10
		PA: (BADI) BASF CORP	
		IN: KILBRIDE, T K	
EP 345717		EP 414115	A 1991-059372/09
		PA: (BADI) BASF AG	
		IN: BUEHLER, V; PETERSEN, H	
		EP 414115	B1 1991-059372/09
		PA: (BADI) BASF AG	
		IN: BUEHLER, V; PETERSEN, H	
		EP 457075	A3 1991-333665/46
		PA: (BADI) BASF AG; (GRIM-I) GRIMMER J	
		IN: GRIMMER, J; KIEFER, H; MARTIN, C	
		US 4994458	A 1991-072935/10
		PA: (BADI) BASF CORP	
		IN: KILBRIDE, T K	
		US 5137732	A 1991-059372/09
		PA: (BADI) BASF AG	
		IN: BUEHLER, V; PETERSEN, H	
EP 345717	A	EP 457075	B1 1991-333665/46
		PA: (BADI) BASF AG; (GRIM-I) GRIMMER J	
		IN: GRIMMER, J; KIEFER, H; MARTIN, C	
	A	EP 1048668	A 2000-681202/62
		PA: (HOFF) HOFFMANN LA ROCHE LTD F; (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) HOFFMANN LA ROCHE & CO KG F	
		IN: NOWOTNY, M; TRITSCH, J	
		EP 1048668	B1 2000-681202/62
		PA: (HOFF) HOFFMANN LA ROCHE LTD F; (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) HOFFMANN LA ROCHE & CO KG F	
		IN: NOWOTNY, M; TRITSCH, J	
US 4977190	A	EP 1296566	B1 2002-154672/22
		PA: (DEGS) DEGUSSA AG	
		IN: BINDER, M; GREISSINGER, D; MOELLER, A; MOLL, M; PFEFFERLE, W; MOLLER, A	
		US 5185336	A 1992-260647/32
		PA: (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) HOFFMANN LA ROCHE INC	
		IN: CAVIEZEL, G; MERTIN, F; TRITSCH, JC; TRITSCH, J	
		US 6368644	B1 2002-154672/22

PA: (DEGS) DEGUSSA AG
IN: BINDER, M; GREISSINGER, D; MOELLER, A; MOLL, M; PFEFFERLE, W
US 6479084 B2 2002-154672/22
PA: (DEGS) DEGUSSA AG
IN: BINDER, M; GREISSINGER, D; MOELLER, A; MOLL, M; PFEFFERLE, W
US 6596327 B2 2002-154672/22
PA: (DEGS) DEGUSSA AG
IN: BINDER, M; GREISSINGER, D; MOELLER, A; MOLL, M; PFEFFERLE, W
US 6723346 B1 2000-681202/62
PA: (HOFF) HOFFMANN LA ROCHE LTD F; (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) HOFFMANN LA ROCHE & CO KG F; (HOFF) ROCHE VITAMINS INC
IN: NOWOTNY, M; TRITSCH, J

L103 ANSWER 9 OF 15 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-748715 [73] WPIX
DOC. NO. CPI: C2004-263148 [73]
TITLE: Rapidly dissolving, high bulk density **granular** **riboflavin** in B/C **modification**, for food or pharmaceutical use, obtained by **precipitation** from aqueous **mineral** **acid** and **fluidized bed** spray **granulation**
DERWENT CLASS: B02; D13
INVENTOR: **FRANKE D**; **HILL F**; **KNEBEL T**; **MARTIN C**
PATENT ASSIGNEE: (BADI-C) BASF AG
COUNTRY COUNT: 107

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2004089889	A2	20041021	(200473)*	DE	15[0]	
DE 10317051	A1	20041021	(200473)	DE		
EP 1615927	A2	20060118	(200606)	DE		
KR 2006006028	A	20060118	(200659)	KO		
CN 1774438	A	20060517	(200663)	ZH		C07D475-00
JP 2006522763	W	20061005	(200667)	JA	18	
US 20060258664	A1	20061116	(200677)	EN		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004089889	A2	WO 2004-EP3689	20040407
DE 10317051	A1	DE 2003-10317051	20030411
CN 1774438	A	CN 2004-80009764	20040407
EP 1615927	A2	EP 2004-726106	20040407
EP 1615927	A2	WO 2004-EP3689	20040407
KR 2006006028	A	WO 2004-EP3689	20040407
JP 2006522763	W	WO 2004-EP3689	20040407
KR 2006006028	A	KR 2005-719236	20051010
JP 2006522763	W	JP 2006-505032	20040407

US 20060258664 A1 WO 2004-EP3689 20040407
US 20060258664 A1 US 2005-552137 20051006

FILING DETAILS:

PATENT NO	KIND		PATENT NO	
EP 1615927	A2	Based on	WO 2004089889	A
KR 2006006028	A	Based on	WO 2004089889	A
JP 2006522763	W	Based on	WO 2004089889	A

PRIORITY APPLN. INFO: DE 2003-10317051 20030411
INT. PATENT CLASSIF.:
IPC ORIGINAL: A61K0031-519 [I,A]; A61K0031-519 [I,C]; A61K0031-525 [I,A]; A61K0009-16 [I,A]; A61K0009-16 [I,A]; B01D0009-00 [I,C]; B01D0009-02 [I,A]; B01J0002-00 [I,A]; B01J0002-16 [I,A]; C07D0475-00 [I,C]; C07D0475-00 [I,C]; C07D0475-02 [I,A]; C07D0475-14 [I,A]
IPC RECLASSIF.: A23L0001-302 [I,A]; A23L0001-302 [I,C]; C07D0475-00 [I,C] ; C07D0475-14 [I,A]

BASIC ABSTRACT:

WO 2004089889 A2 UPAB: 20060122

NOVELTY - The production of **riboflavin** (I) of **modification** B/C in **granular** form comprises: (a) dissolving (I) of **modification** A in aqueous **mineral acid** (b) **precipitating** (I) directly from the solution (without pre-treating with activated carbon); and (c) drying the **precipitate** by **fluidized bed** spray **granulation.**

Stages (a) and (b) are carried out at 5-15degreesC.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (A) (I) in **granular** form, having a bulk density of 0.45-0.7 g/ml (DIN 53468) and a dissolution kinetic value of at least 80% after tableting; and (B) tablets prepared from the claimed form of (I).

USE - (I) (i.e. **vitamin B2**) is used as an active agent or additive in foods or pharmaceuticals.

ADVANTAGE - The process gives pure (I) with good dissolution kinetics (suitable for pharmaceutical or foodstuff applications), good handling properties and a high bulk density. In particular the obtained (I) dissolves rapidly in aqueous media even when pressed into tablets, despite the high bulk density. The **granules** of (I) are free-flowing, non-dusting and free of binders, and can be produced without use of **granulation** auxiliaries. MANUAL CODE: CPI: B03-C; B12-M11B; B12-M11D; D03-H01T

TECH

ORGANIC CHEMISTRY - Preferred Process: The dissolution temperature is 5-12degreesC. (I) is kept in contact with aqueous **mineral acid** for an average of not more than 4 hours (especially not more than 3 hours). **Precipitation** is carried out at 6-12degreesC, preferably continuously, especially in a two-stage stirred vessel cascade, specifically with an average residence time of the (I) solution in the first **precipitation** vessel of 1-10 minutes. Drying is carried out by continuous or semi-continuous **fluidized bed** spray **granulation** in top-spray configuration, preferably at a drying gas inlet temperature of 100-200 (especially 150-170)degreesC. Part of the dried (I) is recycled to the drying process, the weight ratio of recycled (I) to (I) recovered as product being 1-4:1.

Preferred Product: The claimed form of (I) has a bulk density of 0.5-0.65 g/ml and a dissolution kinetic value of at least 85% after tableting; and is preferably free of binders.

L103 ANSWER 10 OF 15 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1992-009838 [02] WPIX

DOC. NO. CPI: C1992-004202 [21]
TITLE: Purifying microbial **riboflavin** by crystal conversion - is performed in water or aqueous acid suspension, giving product of pharmaceutical and food quality
DERWENT CLASS: B02; D13; D16; E13
INVENTOR: GRIMMER J; KIEFER H; **MARTIN C**
PATENT ASSIGNEE: (BADI-C) BASF AG; (GRIM-I) GRIMMER J
COUNTRY COUNT: 8

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
EP 464582	A	19920108	(199202)*	EN		
DE 4021274	A	19920109	(199203)	DE		C07D475-14
CA 2046128	A	19920105	(199214)	EN		
JP 04261176	A	19920917	(199244)	JA	3	C07D475-14
US 5210023	A	19930511	(199320)	EN	3[0]	C12P025-00
EP 464582	A3	19920715	(199334)	EN		
JP 08002903	B2	19960117	(199607)	JA	3[0]	C07D475-14
EP 464582	B1	19960501	(199622)	DE	4[0]	C07D475-14
DE 59107748	G	19960605	(199628)	DE		C07D475-14
CA 2046128	C	20010508	(200129)	EN		C07D475-14

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 464582 A		EP 1991-110432	19910625
DE 4021274 A		DE 1990-4021274	19900704
DE 59107748 G		DE 1991-59107748	19910625
EP 464582 A3		EP 1991-110432	19910625
EP 464582 B1		EP 1991-110432	19910625
DE 59107748 G		EP 1991-110432	19910625
US 5210023 A		US 1991-724056	19910701
CA 2046128 C		CA 1991-2046128	19910703
JP 04261176 A		JP 1991-162568	19910703
JP 08002903 B2		JP 1991-162568	19910703

FILING DETAILS:

PATENT NO	KIND	PATENT NO
DE 59107748 G	Based on	EP 464582 A
JP 08002903 B2	Based on	JP 04261176 A

PRIORITY APPLN. INFO: DE 1990-4021274 19900704
INT. PATENT CLASSIF.:
MAIN: C07D475-14
IPC RECLASSIF.: C07D0475-00 [I,C]; C07D0475-14 [I,A]; C12P0017-18 [I,A]; C12P0017-18 [I,C]

BASIC ABSTRACT:

EP 464582 A UPAB: 20050820 Purification of **riboflavin** (I) produced by fermentation comprises (1) suspending crude (I) in water or dilute aqueous acid; (2) heating with stirring at 75-130 deg.C. for 0.3-3 hr.; then (3) cooling and isolating the crystals formed. Pref. step (2) is at 80-120 deg.C. for 1-2.5 hr., using water, 0.1-1MH2SO4 or 0.1-1.5M H3PO4 or HCl as medium. (I) is suspended in pref. 15-20 pts.weight water, opt. containing 0.05-10 (pref. 0.5-3) weight% of an **inorganic acid.** Where an acidic medium is used, a 96% (I) starting material is

purified to 100%; a 90% material to 97% and a 65% material to 90%. Corresponding figures with water as medium are 99%, 97% and 80%. USE/ADVANTAGE - Microbial (I) is now purified very simply to a product of pharmaceutical/food quality. @(4pp Dwg.No.0/0) MANUAL CODE: CPI: B03-C; B12-J01; D05-C10; D05-H13; E06-D17; E11-Q01

Member(0005)
ABEQ US 5210023 A UPAB 20050820
Purifying ferment-**produced** riboflavin comprises suspending impure riboflavin in water or dilute aq. acid at 10-30 times the wt. of riboflavin without dissolving the riboflavin. Suspension is treated at 75-130 deg.C for 0.3-3 hours with stirring, and the crystals formed on cooling are isolated. Dilute acid is H3PO4 or HCl, at 0.1-1.5 M.
USE/ADVANTAGE - Ferment produced **riboflavin** is purified in an industrially simple manner.

Member(0007)
ABEQ JP 96002903 B2 UPAB 20050820
Purification of **riboflavin** (I) produced by fermentation comprises (1) suspending crude (I) in water or dil. aq. acid; (2) heating with stirring at 75-130 deg.C. for 0.3-3 hr.; then (3) cooling and isolating the crystals formed. Pref. step (2) is at 80-120 deg.C. for 1-2.5 hr., using water, 0.1-1MH2SO4 or 0.1-1.5M H3PO4 or HCl as medium. (I) is suspended in pref. 15-20 pts.wt. water, opt. contg. 0.05-10 (pref. 0.5-3) wt.% of an **inorganic acid.** Where an acidic medium is used, a 96% (I) starting material is purified to 100%; a 90% material to 97% and a 65% material to 90%. Corresponding figures with water as medium are 99%, 97% and 80%.
USE/ADVANTAGE - Microbial (I) is now purified very simply to a product of pharmaceutical/food quality.

L103 ANSWER 11 OF 15 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1989-365498 [50] WPIX
DOC. NO. CPI: C1989-162022 [21]
TITLE: Production of **riboflavin**-containing feed additive **granules** - from fermentation broth by fluidised bed or atomisation drying without addition of binder
DERWENT CLASS: B02; C02; D13; D16; E13
INVENTOR: BUEHLER W; EIPPER G; GRIMMER J; KIEFER H; **MARTIN C**; MEYER J
PATENT ASSIGNEE: (BADI-C) BASF AG
COUNTRY COUNT: 14

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
EP 345717	A	19891213	(198950)*	DE	8[0]	
DE 3819745	A	19891214	(198951)	DE		A23K001-16
DK 8902817	A	19891211	(199010)	DA		
JP 02057188	A	19900226	(199014)	JA		
CN 1038751	A	19900117	(199043)	ZH		
US 4977190	A	19901211	(199101)	EN		C07D471-00
EP 345717	B1	19930512	(199319)	DE	9[0]	A23K001-16
DE 58904314	G	19930617	(199325)	DE		A23K001-16
ES 2040932	T3	19931101	(199348)	ES		A23K001-16
CA 1329361	C	19940510	(199424)	EN		C12P025-00
JP 08029109	B2	19960327	(199617)	JA	4[0]	C12P017-18
DK 174850	B	20031222	(200407)	DA		B01J002-16

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 345717 A		EP 1989-110187	19890606
DE 3819745 A		DE 1988-3819745	19880610
CA 1329361 C		CA 1989-601910	19890606
DE 58904314 G		DE 1989-58904314	19890606
EP 345717 B1		EP 1989-110187	19890606
DE 58904314 G		EP 1989-110187	19890606
ES 2040932 T3		EP 1989-110187	19890606
DK 174850 B		DK 1989-2817	19890609
JP 02057188 A		JP 1989-145546	19890609
JP 08029109 B2		JP 1989-145546	19890609
US 4977190 A		US 1989-363853	19890609

FILING DETAILS:

PATENT NO	KIND	PATENT NO
DK 174850 B	Previous Publ	DK 8902817 A
DE 58904314 G	Based on	EP 345717 A
ES 2040932 T3	Based on	EP 345717 A
JP 08029109 B2	Previous Publ	JP 02057188 A

PRIORITY APPLN. INFO: DE 1988-3819745 19880610
INT. PATENT CLASSIF.:
MAIN: A23K001-16; C12P017-18
IPC RECLASSIF.: A23K0001-00 [I,A]; A23K0001-00 [I,C]; A23K0001-16 [I,A]; A23K0001-16 [I,C]
SECONDARY: A23P001-02 [I,A]; A61K0031-519 [I,C]; A61K0031-525 [I,A]; A61K0009-14 [I,A]; A61K0009-14 [I,C]; C07D0475-00 [I,C]; C07D0475-14 [I,A]; C12P0017-18 [I,A]; C12P0017-18 [I,C]
; A61K0031-519
; C12P025-00

BASIC ABSTRACT:

EP 345717 A UPAB: 20050429 Production of **riboflavin** (I) in the form of free-flowing, non-dusting spray- or micro-**granules** comprises removal of water from the effluent of microbial fermentations for (I) production by (A) spray-fluidised bed drying; (B) single-material nozzle atomisation drying or (c) disc-atomisation drying. No significant amount of binder is added to the fermentation effluent.

In a pref. method, (I) is dry powdered, spray- or micro- **granular** form, is maintained in a fluidised bed drier at 20-150 (pref. 50-100)deg.C, then the fermentation effluent (opt. after enrichment in (I) by decanting) sprayed into the bed at a rate determined by the drying speed. After a suitable dwell time, (I) particles are recovered from the bed and fractionated according to particle size. The 100-250 micron fraction (25-85%) is recovered as product while the fines (6-30%) and, after grinding, oversized particles (1-70%) are recycled to the **granulation** process. The process is pref. operated continuously, particularly using a bed, at 60-80 deg.C, of **granular** (I). Inlet and outlet air temps. are 140-185 deg.C and 60-85 deg.C, respectively.

USE/ADVANTAGE - The **granules** are sued as fodder additives, and are easily formulated without difficulties (e.g. formation of lumps during storage) of conventional products. MANUAL CODE: CPI: B03-C; B12-L09; B12-M11D; C03-C; C12-L09; C12-M11D; D03-G01; E06-D17

Member(0006)
ABEQ US 4977190 A UPAB 20050429

Prepn. of **riboflavin**, produced by microbial method, in the form of free-flowing, non-dusting, **spray**-dried granules or microgranules, which comprises removing water from mixt. discharged from the microbial fermentation. The discharged mixt. is subjected to drying process selected from fluidised-bed soray-drying process, one-material spray-drying process, and disc spray-drying process, in the absence of significant amts. of binders being added to discharged mixts..
Pref. process is by fluidised-bed spray-drying.
USE - Free-flowing, non-dusting **riboflavin**-contg. **granules** are obtd. without the addn. of binders, which are easy to handle. @(5pp)

Member(0011)
ABEQ JP 96029109 B2 UPAB 20050429
Prodn. of **riboflavin** (I) in the form of free-flowing, non-dusting spray- or micro-**granules** comprises removal of water from the effluent of microbial fermentations for (I) prodn. by (A) spray-fluidised bed drying; (B) single-material nozzle atomisation drying or (c) disc-atomisation drying. No significant amt. of binder is added to the fermentation effluent.
In a pref. method, (I) is dry powdered, spray- or micro-**granular** form, is maintained in a fluidised bed drier at 20-150 (pref. 50-100)deg.C, then the fermentation effluent (opt. after enrichment in (I) by decanting) sprayed into the bed at a rate determined by the drying speed. After a suitable dwell time, (I) particles are recovered from the bed and fractionated according to particle size. The 100-250 micron fraction (25-85%) is recovered as product while the fines (6-30%) and, after grinding, oversized particles (1-70%) are recycled to the **granulation** process. The process is pref. operated continuously, particularly using a bed, at 60-80 deg.C, of **granular** (I). Inlet and outlet air temps. are 140-185 deg.C and 60-85 deg.C, respectively.
USE/ADVANTAGE - The **granules** are sued as fodder additives, and are easily formulated without difficulties (e.g. formation of lumps during storage) of conventional products.

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L103 ANSWER 12 OF 15 USPATFULL on STN
ACCESSION NUMBER: 2006:302304 USPATFULL Full-text
TITLE: Method for the production of **riboflavin** of **modification b/c** in **granular** form
INVENTOR(S): **Franke, Dirk**, Birkenheide, GERMANY, FEDERAL REPUBLIC OF
Hill, Friedrich, Meckenheim, GERMANY, FEDERAL REPUBLIC OF
Martin, Christoph, Mannheim, GERMANY, FEDERAL REPUBLIC OF
Knebel, Thomas, Schifferstadt, GERMANY, FEDERAL REPUBLIC OF
PATENT ASSIGNEE(S): BASF AKTIENGESELLSCHAFT, Ludwigshafen, GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2006258664	A1	20061116	
APPLICATION INFO.:	US 2004-552137	A1	20040407	(10)

WO 2004-EP3689 20040407
20051006 PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	DE 2003-10317051	20030411

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CONNOLLY BOVE LODGE & HUTZ, LLP, P O BOX 2207, WILMINGTON, DE, 19899, US
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
LINE COUNT: 545
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to an improved process for preparing pure **riboflavin** (**vitamin B2**) of the **B/ C modification** in **granule** form. Furthermore, the invention relates to pure **riboflavin** in **granule** form which has a bulk density to be determined in accordance with DIN 53468 of from 0.45 to 0.7 g/ml and, after tableting, has a dissolution of at least 80%.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Method for the production of **riboflavin** of **modification b/c** in **granular** form

IN **Franke, Dirk**, Birkenheide, GERMANY, FEDERAL REPUBLIC OF
IN **Hill, Friedrich**, Meckenheim, GERMANY, FEDERAL REPUBLIC OF
IN **Martin, Christoph**, Mannheim, GERMANY, FEDERAL REPUBLIC OF
IN **Knebel, Thomas**, Schifferstadt, GERMANY, FEDERAL REPUBLIC OF

AB The present invention relates to an improved process for preparing pure **riboflavin** (**vitamin B2**) of the **B/ C modification** in **granule** form. Furthermore, the invention relates to pure **riboflavin** in **granule** form which has a bulk density to be determined in accordance with DIN 53468 of from 0.45 to 0.7 g/ml and, after tableting, has a dissolution of at least 80%.

SUMM The present invention relates to an improved process for preparing pure **riboflavin** (**vitamin B2**) of the **B/ C modification** in **granule** form. In addition, the invention relates to pure **riboflavin** in **granule** form, which features particularly good dissolution at high bulk density.

SUMM When **riboflavin** (**vitamin B2**) is used which is intended as an active ingredient or additive for foods or pharmaceuticals, very high demands on the purity of the product have to be fulfilled. This constitutes one of the main requirements on the currently conducted synthetic or biotechnological processes for industrially preparing **riboflavin**.

SUMM In general, **riboflavin** prepared by biotechnological processes occurs in an initial purity of about 75%, which is attributed mainly to impurities which are typical of biotechnological preparative processes, for instance cell residues, proteins, peptides or else amino acids. Such crude products are therefore unsuitable for the aforementioned applications in humans and require further purification.

SUMM For some time, there has existed a need for an economic process which enables highly pure **riboflavin** having satisfactory solubility properties to be prepared. The main emphasis is on processes for preparing **riboflavin** in the B and/or C **modifications**, especially **riboflavin** which is substantially in the **B modification** and may comprise small amounts of **riboflavin** of the C

modification, which is difficult to detect (referred to hereinbelow as **riboflavin** of the **B/C modification**).

SUMM A first approach to this aim is described by EP-A 0 307 767: to prepare a spherulitic form of **riboflavin** having improved handling and flow properties, **riboflavin** is dissolved in a solvent and is precipitated using a second solvent in which **riboflavin** is insoluble but which is miscible with the first solvent.

SUMM EP-A 0 457 075 describes a process for preparing very free-flowing, nondusting and binder-free **riboflavin** spray **granules** or microgranuies from pure **riboflavin.** In this process, an aqueous or water-containing suspension of pure, finely divided **riboflavin** is subjected to spray fluidized bed drying, to single-material nozzle atomization drying or to disk atomization drying.

SUMM EP-A 0 995 749 describes a purification and crystallization process for **riboflavin.** In this process, **riboflavin** of the A modification is dissolved in aqueous mineral acid and purified by admixing with activated carbon. After a filtration, the material of value is precipitated by adding water in the method described by EP-A 0 307 767 and isolated. This gives dendritic spherical crystals of the **B/C modification.**

SUMM EP-A 1 048 668 describes a process which is based on the teaching of EP-A 0 457 075 and prepares nondusting and binder-free **riboflavin granules** having good flow properties. In this process, the **riboflavin**, as described in EP-A 0 995 749, is initially purified by activated carbon and, after a subsequent crossflow filtration, precipitated at a temperature of from 0 to 30° C. Afterwards, the aqueous **riboflavin** suspension obtained in this way is filtered and washed, and the **riboflavin** of the **B/C modification** isolated in this way is subjected to spray fluidized bed drying, to single-material nozzle atomization drying or to disk atomization drying.

SUMM **Granules**, as described, for example, in EP-A 1 048 668, are generally notable for good solubility properties, but have a low bulk density, which considerably complicates their handling and further processing.

SUMM There is therefore still a need for a process for preparing pure **riboflavin** which, in combination with good dissolution kinetics which are sufficient for pharmacological and food technology applications, has generally good handling properties and in particular a high bulk density.

SUMM A process has now been found for preparing **riboflavin** of the **B/C modification** in **granule** form, which comprises

a) dissolving **riboflavin** of the A modification in aqueous mineral acid,
b) directly afterwards, without initially treating the resulting **riboflavin** solution in mineral acid with activated carbon, precipitating, steps a) and b) being carried out at a temperature in the range from 5 to 15° C., and
c) drying the **riboflavin** by fluidized bed spray **granulation**

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SUMM The **riboflavin granules** prepared in this way are notable for particularly advantageous dissolution kinetics and a high bulk density. The properties of the **granules** are such that they can be dissolved rapidly in aqueous media even after pressing to tablet form (tableting), in spite of their high density.

SUMM In addition to the low dissolution temperature of the preparative process according to the invention, this particularly advantageous combination of properties also depends upon how long the **riboflavin** comes into contact with the mineral acid medium used as a solvent. A shortening of the contact time leads to an improvement in the inventive product properties. The shortening of the contact time of **riboflavin** and mineral acid medium is achieved in the process according to the invention, among other measures, by omitting the time-consuming purification step of adding activated carbon, and carrying out the precipitation immediately after the dissolution procedure. In this context, immediately means that no further process steps or prolonged lifetimes of the solution are envisaged between dissolution procedure and precipitation which go beyond the necessary transport of the solution from the dissolution tank to the first precipitation tank, for example through pipelines. Nor is it necessary to use other adsorbents familiar per se to those skilled in the art.

SUMM The limiting of the contact time of the **riboflavin** with the mineral acid dissolution medium results in the decomposition products which are always formed in traces on treatment with acid being generated to a relatively slight extent, which, after precipitation and final fluidized bed spray **granulation**, leads to the particularly advantageous properties of the inventively prepared **granular riboflavin.** It is thus the combination of the process features illustrated which leads to the advantageous properties of the **riboflavin granules** according to the invention.

SUMM The process according to the invention is suitable for preparing pure **riboflavin** of the **B/C modification** in **granule** form. The starting substance used is **riboflavin** which has been prepared synthetically or by fermentation, but preferably by fermentation, and, after the preparation, has optionally already passed through at least one purification step, for example by reprecipitation, and has a purity which is typically in the range from 90 to 99%. A preferred starting material is **riboflavin** having a purity of from 95 to 99%, more preferably having a purity of from 97 to 99%. This is typically completely or predominantly (i.e. more than about 90%) present in the A modification, but can in principle be used in any desired modification.

SUMM According to the invention, the **riboflavin** serving as a starting substance is dissolved in aqueous mineral acid, for example in nitric acid or, preferably, in hydrochloric acid. The concentration of the mineral acid is typically from about 10 to about 65% by weight. The aqueous hydrochloric acid preferably used as the dissolution medium appropriately has a concentration in the range from about 18 to about 28% (% by weight).

SUMM The dissolution procedure in the process according to the invention is effected at a temperature of the dissolution medium in the range from about 5° C. to about 15° C. Preference is given to dissolution temperatures in the range from 5° C. to 12° C., most preferably from 6° C. to 9° C. This gives

solutions in which up to about 20% by weight **riboflavin** is dissolved. In general, the dissolution procedure is complete after from 30 to 150 min.

SUMM The duration of the dissolution procedure is selected in such a way that the overall time during which the **riboflavin** is in contact with the mineral acid solvent is very short. In this context, the overall contact time is the time from the beginning of the dissolution procedure until precipitation of the **riboflavin** from the aqueous hydrochloric acid dissolution medium, i.e. the time during which the **riboflavin** is dissolved in the aqueous hydrochloric acid dissolution medium. It is advantageous to work with overall contact times up to about 4 h. Particular preference is given to overall contact times from about 2.5 to about 3 h. Since the process according to the invention preferably also includes continuous process steps, the contact times specified, like all further time data (for example dissolution or precipitation time), are to be interpreted as average times.

SUMM For precipitation, the mineral acid **riboflavin** solution is admixed with water, typically with from about five to ten times the amount (v/v). In the case of aqueous hydrochloric acid, which is preferably used as a solvent in accordance with the invention, preference is given to adding sufficient water to obtain a hydrochloric acid concentration of from about 1.5 to about 4% by weight, preferably from about 2 to about 3% by weight.

SUMM The **riboflavin** can be precipitated continuously or batchwise in one or more stirred tanks connected in series, known as a stirred tank battery. In a preferred embodiment of the process according to the invention, the precipitation is carried out continuously in a two-stage stirred tank battery.

SUMM The average residence times of the **riboflavin** solution in the inventively preferred, continuous precipitation of the **riboflavin** in the first stirred tank are in the range from about 1 min to about 10 min, preferably from about 2.5 min to about 5 min. The residence time in the second tank can vary more widely, but is appropriately selected within the range from about 5 to about 15 min, preferably from about 5 min to about 10 min.

SUMM The **riboflavin** which can be prepared by the process steps according to the invention is in the form of agglomerates. These have a high density and a smooth surface and feature, in particular with regard to the further processing which is typically also necessary, considerable advantages compared to conventional spherical **riboflavin** crystals. The conventional crystals sometimes have a spiny surface (see EP-A 0 995 749) and have low shear stability. This property, which is unfavorable for the process control, promotes the growth of needle-shaped crystals and leads, inter alia, to poor process stability and to poor filtration and handling properties.

SUMM The process control of the precipitation can be used to influence the agglomerate formation. In the case of continuous operation with two tanks, care has to be taken that the feed streams are metered precisely. The mixing times should be short, in order to prevent localized overconcentrations. The latter can be achieved by suitable choice of the stirrer and also of the metering points, as familiar to those skilled in the art. It may possibly be advantageous to divide the feed of water and **riboflavin** solution to the vessels. However, not more than 70%

of the water should be added to the second reactor. A further possibility for concentration adjustment is offered by the recycling of suspension from the second precipitation vessel, and also the recycling of mother liquor after the filtration. This means that the solids concentration can be freely selected, which influences the agglomeration kinetics. When the suspensions are removed from the reactor, it is to be noted that this can also result in changes in the solids concentration in the reactor. This can also result in changes in the agglomeration kinetics. The particle size of the agglomerates changes as a function of the dispersion in the pipelines, which likewise influences the available surface area.

SUMM The advantageous version of the precipitation step may differ between pilot plant and operation scale. When the process according to the invention is carried out on the industrial scale, the product properties which are advantageous compared to the prior art arise particularly distinctly when the process steps connected in series are in a steady state. This state is attained typically after about 10 cycles. In the process carried out on a smaller scale, for example on the laboratory or pilot plant scale, it may be possible and advantageous to further reduce the overall contact time of the **riboflavin** with the aqueous mineral acid dissolution medium.

SUMM Afterwards, the precipitated **riboflavin** is removed from the aqueous precipitation medium by filtration methods which are familiar per se to those skilled in the art, and washed.

SUMM The filtercake obtainable by the filtration, consisting of solid **riboflavin** of the **B/C modification** , is advantageously suspended by adding water. The amount of the water added is selected in such a way that a **riboflavin** suspension having a solids content of from about 5 to about 15% by weight, preferably from about 8 to about 12% by weight, is obtained. However, it is also possible to use a suspension in a solvent having not too high a boiling point when this solvent comprises water. The water content in the suspension should then be at least 10% by weight. Useful solvents are in particular water-miscible solvents, for example C.sub.1- to C.sub.4-alkanols.

SUMM For drying, the **riboflavin** suspension is subjected to a fluidized bed spray **granulation.** In contrast to the known spray drying of **riboflavin** solutions or suspensions, in which they are typically sprayed into the drying tower by means of a two-material nozzle, the suspension in the fluidized bed spray **granulation** employed in accordance with the invention is sprayed continuously or batchwise into a fluidized bed of dry reaction product. The drying unit is provided with apparatus which allows a certain particle size fraction to be obtained and the **granulation** process to be maintained (cf. K. Kroll, Trocknungstechnik [drying technology], Volume II, "Trockner und Trocknungsverfahren" ["dryers and drying processes"], Springer, Berlin, 1978, 221-223).

SUMM It is advantageous to work in a continuous spray fluidized bed (cf. H. Uhlemann, "Wirbelschichtspruhgranulation" ["fluidized bed spray **granulation**"], Springer, 2000, 219-244) with integrated filter and a nozzle arrangement which allows the **riboflavin** suspension to be sprayed from above onto or into the fluidized bed (known as the "top-spray process").

SUMM To carry out the fluidized bed spray **granulation** according to

the invention, the procedure is generally to

a) initially charge **riboflavin** in the form of a dry powder or of spray or microgranules in a fluidized bed dryer, in a fluidized bed heated to from 20 to 100° C., preferably from 50 to 100° C., in particular from 65 to 95° C.,
b) add to this an aqueous or water-containing suspension of the finely divided **riboflavin** in sprayed form as a function of the drying rate,
c) remove the **riboflavin** particles from the fluidized bed after a suitable residence time and separate them into particle fractions using a suitable apparatus,
d) discharge the particle fraction in the particle size range from about 50 to about 450 μm, preferably from about 80 to about 250 μm and
e) recycle the more finely divided particles and/or the more finely divided particles obtained by grinding larger particles and/or a portion of the fraction discharged as the useful fraction with or without grinding into the spray fluidized bed.

SUMM To carry out the process, a **riboflavin** product first has to be prepared from the dry **riboflavin** powder corresponding to the prior art which is suitable for generating a fluidized bed. In the batchwise procedure, a sufficiently finely divided product, as obtained, for example, by spray drying or agglomerating spray drying, can be initially charged in the fluidized bed. Depending on the residence time of the particles in the spray fluidized bed, a dry product is then obtained which has a smaller or larger particle size range. Particles in the size range from about 50 to 450 μm have the desired properties and are therefore obtained as the product of value. Smaller particles, and also **riboflavin** obtained by grinding larger particles, are used as fluidized bed material for further batches.

SUMM To carry out the continuous process, the aqueous or water-containing suspension of finely divided **riboflavin** is sprayed continuously into a fluidized bed. The rate of the spray introduction is set in such a way that the fluidized bed has a temperature corresponding to the desired degree of drying. The temperature is determined by the difference between inlet and outlet temperature of the fluidizing gas blown into the dryer.

SUMM In continuous process control, when the fluidized bed dryer is started up for the first time, the starting material in the fluidized bed is finely divided **riboflavin.** Afterwards, a dry product is obtained which has virtually constant particle size distribution. From this it is advantageous to remove, continuously or intermittently, a certain portion of the desired particle size fractions. The particle fraction in the particle size range from about 50 to about 450 μm is discharged as a product of value and the finely divided particles and/or the finely divided particles obtained by grinding larger particles are recycled continuously into the fluidized bed to maintain the **granulation** process.

SUMM The amount of **riboflavin** corresponding to the amount removed as the product of value is sprayed into the fluidized bed continuously in the form of an aqueous suspension of finely divided **riboflavin**, thus keeping the amount of **riboflavin** in the fluidized bed constant.

SUMM The evaporation of the amount of liquid introduced into the fluidized bed with the aqueous **riboflavin** suspension can require the

supply of additional energy. To this end, for example, heating surfaces can be immersed in the fluidized bed. The temperature of the heating surfaces is typically in the range from 100 to 250° C., preferably in the range from 140 to 180° C.

SUMM The process described is suitable for preparing pure **riboflavin** of the **B/C modification** in **granule** form. In this context, pure **riboflavin** is **riboflavin** which has a degree of purity of more than 96%, preferably of more than 98%, more preferably of more than 99%, and has not been admixed with binding or **granulating** auxiliaries or other additives.

SUMM The invention further relates to pure **riboflavin** in **granule** form which has a bulk density of from 0.45 to 0.7 g/ml and, after tableting, has a dissolution of at least 80%. The invention preferably relates to pure **riboflavin** in **granule** form which has a bulk density of from 0.5 to 0.65 g/ml and, after tableting, has a dissolution of at least 80%. The invention more preferably relates to pure **riboflavin** in **granule** form which has a bulk density of from 0.5 to 0.65 g/ml and, after tableting, has a dissolution of at least 85%.

SUMM In this context, bulk density is the quotient of the mass and the volume which is taken up by a material which can assume shape (in this case **riboflavin** in **granule** form) and is poured in a certain manner.

SUMM The determination of the bulk density of the **riboflavin** according to the invention in **granule** form, and also **riboflavin** products or administration forms of **riboflavin** which have been obtained in a different way and are to be compared thereto, is to be carried out in accordance with DIN 53468 (November 1960).

SUMM Surprisingly, the inventive **riboflavin** in **granule** form, even after tableting, i.e. after compression to tablet form, exhibits surprisingly good dissolution kinetics.

SUMM To tablet the inventive **riboflavin** in **granule** form, and also **riboflavin** products which have been obtained in other ways and are to be compared thereto, a powder mixture consisting of 16.66% by weight of **riboflavin**, 53.34% by weight of Tablettose (Meggle AG), 26.84% by weight of Avicel® PH 102 (FMC Corp.), 0.5% by weight of Ac-Di-Sol® (FMC Corp.), 2.0% by weight of Aerosil® 200 (Degussa AG) and 0.66% by weight of magnesium stearate (Barlocher GmbH) is initially prepared. To this end, all the ingredients, with the exception of the **riboflavin** and also of the magnesium stearate, are intimately mixed for 10 min in a Turbula mixer and subjected to forced sieving through a sieve of mesh width 0.8 mm, the **riboflavin** and the magnesium stearate are added, and the mixture is mixed in the Turbula mixer for another 10 min. The powder mixture prepared in this way is compressed with a Korsch PH 106 tablet press at a tableting rate of 20 revolutions/min and a compressive-force of 10 kN to give beveled, biplanar tablets having a diameter of 8 mm, a weight of 300 mg and a **riboflavin** content of 50 mg.

SUMM A suitable measure for determining the dissolution kinetics of the **riboflavin granules** according to the invention after the tableting carried out as described above is the dissolution.

SUMM To determine the dissolution of the tableted **riboflavin**, a fully automatic release instrument according to U.S.P. 26 (Physical Tests/711 Dissolution, p. 2155) is used. The measurement is carried out in a 1 liter measuring cylinder which is filled with 900 ml of 0.1 molar hydrochloric acid. The measurement solution is heated in a water bath to from 36.5 to 37.5° C. and stirred with a paddle stirrer at 75 revolutions/min. 30 minutes after addition of the **riboflavin** tablet prepared as described above, a sample of the measurement solution is taken whose **riboflavin** content, optionally after further dilution, is determined by UV spectroscopy at a wavelength of 267 nm. The proportion of the amount of **riboflavin** released from the tablet after 30 min is reported in [%] as the dissolution.

SUMM The combination of the properties mentioned, which has hitherto not been achieved, makes the inventive **riboflavin granules** superior to the administration forms of **riboflavin** known hitherto. At the same time, the inventive **granules** are very free-flowing, nondusting and binder-free. They are preferably obtained without adding **granulating** auxiliaries.

DETD General Method for Preparing **Riboflavin** in **Granule** Form

DETD 100 kg of an aqueous solution which has been prepared at the dissolution temperature X (see Table 1) and comprises 10% by weight of **riboflavin** and 22% by weight of HCl are introduced continuously into a stirred tank at a rate of 48 kg/h together with 360 l/h of water. The solution remains there at a temperature of 8° C. and an introduced stirrer output of approx. 0.12 W/l at an average residence time of 4:30 min for precipitation. After a further residence time of approx. 6 min in a downstream stirred tank, the resulting suspension is filtered through a belt filter and the residue is washed with water. In this way, an overall contact time of the **riboflavin** with the hydrochloric acid dissolution medium of about 2:30 h is attained.

DETD An aqueous suspension which comprises about 10% by weight of this residue is sprayed from above onto the fluidized initial charge of a fluidized bed dryer at a rate of 4 kg/h and an air feed temperature of 180° C. by means of a two-material nozzle. During the experiment, **granules** are removed from the product chamber, so that the contents of the fluidized bed remain constant. The effluent is fractionated with a sieve (250 μm). The coarse material is comminuted using a universal mill and reintroduced to the fluidized bed, the ratio of recycled to discharged product being 1:1.

TABLE 1

Experiment	Dissolution temperature X [° C.]	[%]	Dissolution [g/ml]	Bulk density
Experiment 1	12		86	0.57
Experiment 2	8		89	0.57
Comparative experiment 1	3		--/--*	--/--*
Comparative experiment 2	22		78	0.61

*strongly dusting product which could not be **granulated**

DETD Drying of **Riboflavin** Suspensions Prepared According to Example 1 on the Industrial Scale

DETD The spray **granulation** is effected in a fluidized bed apparatus having an incident flow surface area of 0.07 m.sup.2. The flow

rate of the suspension sprayed in is between about 12 and 20 kg/h. The product chamber of the fluidized bed apparatus is provided with heating surfaces heated to 160° C. The fluidization gas is blown in at a temperature of 166° C. For particle size control, a portion of the fluidized material is removed and separated with a sieve machine into two fractions (useful fraction <250 µm, coarse fraction >250 µm). The coarse fraction and, if required, a portion of the useful fraction, are ground and recycled into the fluidized bed. The ratio of recycled to discharged product is given by the values under "recycling" in Table 2.

TABLE 2

Experiment	Recycling	Dissolution [%]	Bulk density [g/ml]
Experiment 3	1:1	83	0.56
Experiment 4	2.1:1	88	0.54

DETD Bulk Densities and Dissolution Values of **Riboflavin Granules**

DETD

TABLE 3

Sample	Dissolution [%]	Bulk density [g/ml]
Riboflavin Tablet Grade (F. Hoffmann-La Roche AG)	78	0.388
Inventive **riboflavin** in **granule** form	90	0.501
Riboflavin High Flow 95 (Takeda Ltd.)	85	0.385
Riboflavin 100 (BASF Aktiengesellschaft)	73-75	0.350

CLM What is claimed is:

1. A process for preparing **riboflavin** of the **B/C modification** in **granule** form, wherein **riboflavin** of the A modification a) is dissolved in aqueous mineral acid, b) is precipitated directly afterwards, without initially treating the resulting **ribo-flavin** solution in mineral acid with activated carbon, steps a) and b) being carried out at a temperature in the range from 5 to 15° C., and c) the **riboflavin** is dried by fluidized bed spray **granulation**, and wherein the **riboflavin** does not come into contact with the aqueous mineral acid solvent for longer than on average 4 h.

3. The process according to claim 1, wherein the **riboflavin** does not come into contact with the aqueous mineral acid solvent for longer than on average 3 h.

7. The process according to claim 1, wherein the precipitation is carried out in the first stirred tank of the two-stage stirred tank battery with an average residence time of the **riboflavin** solution in the first stirred tank of from 1 to 10 min.

8. The process according to claim 1, wherein drying is carried out using a continuous or semicontinuous fluidized bed spray **granulation** in top-spray con-figuration.

9. The process according to claim 1, wherein the temperature of the dry gas blown into the dryer in the fluidized bed spray **granulation**

is in the range from 100 to 200° C.

10. The process according to claim 1, wherein the temperature of the dry gas blown into the dryer in the fluidized bed spray **granulation** is in the range from 150 to 170° C.

12. The process according to claim 2, wherein the **riboflavin** does not come into contact with the aqueous mineral acid solvent for longer than on average 3 h.

16. The process according to claim 6, wherein the precipitation is carried out in the first stirred tank of the two-stage stirred tank battery with an average residence time of the **riboflavin** solution in the first stirred tank of from 1 to 10 min.

17. The process according to claim 7, wherein drying is carried out using a continuous or semicontinuous fluidized bed spray **granulation** in top-spray con-figuration.

18. The process according to claim 8, wherein the temperature of the dry gas blown into the dryer in the fluidized bed spray **granulation** is in the range from 100 to 200° C.

19. The process according to claim 9, wherein the temperature of the dry gas blown into the dryer in the fluidized bed spray **granulation** is in the range from 150 to 170° C.

20. The process according to claim 10, wherein a portion of the **riboflavin** obtained after the drying is recycled back into the drying process, and the ratio of the stream recycled into the spray fluidized bed to the stream which is removed from the process as the product of value is from about 1:1 to about 4:1.

IT **Granulating** apparatus
(fluidized bed; procedure for the production of **riboflavin** of the **modification B/C** in **granular** form.)
IT Drying
(fluidized-bed; procedure for the production of **riboflavin** of the **modification B/C** in **granular** form.)
IT Fluidized beds
(**granulating** apparatus; procedure for the production of **riboflavin** of the **modification B/C** in **granular** form.)
IT Acids, biological studies
(inorg.; procedure for the production of **riboflavin** of the **modification B/C** in **granular** form.)
IT Binders
IT Precipitation (chemical)
IT Tablets
(procedure for the production of **riboflavin** of the **modification B/C** in **granular** form.)
IT **Granulation**
(spray **granulation**; procedure for the production of **riboflavin** of the **modification B/C** in **granular** form.)
IT **83-88-5P, Riboflavin**, biological studies

(procedure for the production of **riboflavin** of the **modification B/C** in **granular** form.)

L103 ANSWER 13 OF 15 USPATFULL on STN
ACCESSION NUMBER: 94:28551 USPATFULL Full-text
TITLE: Spray **granules** or microgranules of pure **riboflavin** which contain no binder are non-dusting and free-flowing, and the preparation thereof
INVENTOR(S): Grimmer, Johannes, Ludwigshafen, Germany, Federal Republic of
Kiefer, Hans, Wachenheim, Germany, Federal Republic of
Martin, Christoph, Mannheim, Germany, Federal Republic of
PATENT ASSIGNEE(S): BASF Aktiengesellschaft, Ludwigshafen, Germany, Federal Republic of (non-U.S. corporation)

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NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
LINE COUNT: 323
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A process for preparing spray **granules** or microgranules, which contain no binder, are non-dusting and free-flowing, from finely divided pure **riboflavin**, comprises subjecting an aqueous or water-containing suspension of the pure finely divided **riboflavin** to

a) a fluidized bed spray drying

b) a single-nozzle spray drying or

c) a disk-type spray drying

in particular a fluidized bed spray drying, without adding binders to the suspension, and the spray **granules** or microgranules of **riboflavin** obtainable by this process.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Spray **granules** or microgranules of pure **riboflavin** which contain no binder are non-dusting and free-flowing, and the

preparation thereof

IN **Martin, Christoph**, Mannheim, Germany, Federal Republic of

AB A process for preparing spray **granules** or microgranules, which contain no binder, are non-dusting and free-flowing, from finely divided pure **riboflavin**, comprises subjecting an aqueous or water-containing suspension of the pure finely divided **riboflavin** to

AB in particular a fluidized bed spray drying, without adding binders to the suspension, and the spray **granules** or microgranules of **riboflavin** obtainable by this process.

SUMM The present invention relates to spray **granules** or microgranules of pure **riboflavin** which contain no binder, are non-dusting and free-flowing, and to a process for the preparation thereof from finely divided pure **riboflavin**.

SUMM **Riboflavin** (**vitamin B2**) is used widely in the foodstuffs and drugs industries as an essential or else only coloring additive to food products and drugs. When prepared by synthesis or obtained biotechnologically it is partly in the form of very finely divided powders and partly in the form of long yellow needles. Both types of **riboflavin** have very poor handling and flow properties.

SUMM For example, the finely divided powder is prone to dusting, has a very low bulk density (usually below 0.2 g/ml) , easily picks up an electrostatic charge, flows poorly and therefore can be further processed only with great difficulty. Another serious disadvantage of the finely divided powder is that it cannot be used to produce tablets with a **riboflavin** content exceeding 25% by weight (cf. V. Buhler, "Vademecum for Vitamin Formulations", Wissenschaftliche Verlagsgesellschaft, Stuttgart, pages 98 to 99).

SUMM The **riboflavin** in the form of needles obtainable by slow crystallization at elevated temperature also gives rise to problems, because it flows poorly and because of the formation of dust and acquisition of charge, in further processing such as, for example, in the vitaminization of flour or on tableting.

SUMM In order to solve these problems, **riboflavin** has been partially **granulated** with the addition of auxiliaries in order to obtain a product which has acceptable flow and compression properties. Thus, EP-A-02 19276 describes vitamin-containing **granules** which contain 90-99 % vitamin and a binder.

SUMM Although these **granules** are very suitable for further industrial processing, whether for direct tableting or for preparing other **riboflavin**-containing drug products or human or animal foods containing **vitamin B2**, it is often unsatisfactory that they are not composed of pure active substance. This applies particularly to drug products because the pharmacopeia specifies a **riboflavin** with a minimum content of 98%.

SUMM In order to obtain **riboflavin** containing no binder for the drugs industry, in the process of EP-A-0 307 767 **riboflavin** is dissolved in a solvent and precipitated using a second solvent in which **riboflavin** is insoluble but which is miscible with the first solvent to give spherulitic crystals with good handling properties. However, this process is difficult to carry out industrially and is costly because large amounts of solvent are used and the resulting solvent mixtures have to be reprocessed.

SUMM It is an object of the present invention to develop a process which can be used to prepare from finely divided pure **riboflavin** in an industrially straightforward manner **riboflavin** **granules** which contain no binder and have properties making them easy to use industrially, i.e. **granules** which, on the one hand, are low-dusting, flow well, have a maximum bulk density and minimum electrostatic charge but, on the other hand, can be very finely divided again in a straightforward manner during further processing.

SUMM We have found that this object is achieved by the fluidized bed spray drying of an aqueous or water-containing suspension of finely divided pure **riboflavin.**

SUMM The present invention relates to a process for preparing spray **granules** or microgranules, which contain no binder, are non-dusting and free-flowing, from finely divided pure **riboflavin**, which comprises subjecting an aqueous or water-containing suspension of the pure finely divided **riboflavin** to

SUMM The process according to the invention is particularly advantageous when the aqueous or water-containing suspension of pure finely divided **riboflavin** is subjected to a fluidized bed spray drying.

SUMM The present invention also relates to spray **granules** or microgranules of pure **riboflavin** which contain no binder, are non-dusting and free-flowing, as are obtained by the process according to the invention.

SUMM The starting material used for the process according to the invention is finely divided pure **riboflavin** as obtained by prior art methods, for example by simply spray drying an aqueous suspension of **riboflavin** or else by rapid precipitation from acidified aqueous **riboflavin** solutions at below about 50° C., preferably 20° to 30° C., or else by rapid precipitation and rapid cooling of hot aqueous **riboflavin** solutions at a pH of from 0.8 to 6.5. This finely divided **riboflavin** normally has an average maximum particle diameter of about 0.1 to 50 μm, preferably 10 to 30 μm, and a bulk density of less than 0.2 g/ml.

SUMM **Riboflavin** in the form of larger needles, as is obtained,, for example, in the purification of crude **riboflavin** by the method of DE-A-3 421 714 by slow precipitation of **riboflavin** from acidic aqueous solutions at from 90° to 100° C., is not suitable in the form of its suspension as starting material for the process according to the invention. However, **riboflavin** in the form of larger needles which is obtained by slow precipitation at above 50° C. can be converted into suitable finely divided **riboflavin** by reprecipitation or by wet milling (e.g. in a colloid mill).

SUMM Pure **riboflavin** according to the invention is **riboflavin** with a purity of from 96 to 100, preferably 98 to 100, % and to which none of the conventional binders or **granulating** auxiliaries has been added.

SUMM The finely divided pure **riboflavin** is advantageously employed in the form of an aqueous suspension containing from 5 to 30, preferably 15 to 25, % by weight **riboflavin.** However, it is also possible to employ a suspension in a solvent which does not have too high a

boiling point if this solvent contains water. The water content in the suspension should then be not less than about 10% by weight. Particularly suitable solvents are water-miscible solvents such as, for example, C.sub.1 -C.sub.4 -alkanols.

SUMM In contrast to the known spray drying of **riboflavin** solutions or suspensions, in which the latter are normally sprayed by means of a two-fluid nozzle into a drying tower, in the fluidized bed spray drying employed according to the invention the suspension is sprayed continuously or discontinuously into a fluidized bed of dry product. The drier is equipped with suitable apparatus to allow a defined particle size fraction to be obtained and the **granulation** process to be maintained (cf. K. Kroll, Trocknungstechnik, volume II "Trockner und Trocknungsverfahren", 2nd edition, Springer-Verlag, Berlin, 1978, pages 221 to 223). It is advantageous to use a spray drier having an integral fluidized bed (abbreviation: FSD=Fluidized Spray Drier) as described in Chem.-Ing.-Tech. 59 (1987) No. 2,pp. 112-117, especially page 115.

SUMM The fluidized bed spray drying, according to the invention, of **riboflavin** suspensions is generally carried out by

SUMM a) introducing **riboflavin** in the form of a dry powder or of spray **granules** or microgranules into a fluidized bed drier in which the bed is kept at from 20° to 100° C., preferably 50° to 90° C., in particular 60° to 80° C.,

SUMM b) adding to this an aqueous or water-containing suspension of the finely divided **riboflavin** in sprayed form in accordance with the rate of drying,

SUMM c) after a suitable residence time, drawing off the **riboflavin** particles from the fluidized bed and separating them into fractions in a suitable apparatus,

SUMM e) returning the finer particles and/or the fine particles obtained by milling larger particles to the **granulation** process.

SUMM To carry out the process it is initially necessary to prepare from dry **riboflavin** powder of the prior art a product which can be used to produce a fluidized bed. When the process is carried out discontinuously, a relatively finely divided product can be placed in the fluidized bed. The particle size range of the resulting dry product depends on the residence time of the particles in the drier. Particles in the size range from about 50 to 450 μm have the desired handling properties and are therefore the required product. Smaller particles, and **riboflavin** obtained by suitable milling of larger particles, are used as fluidized bed material for further batches.

SUMM To carry out the process continuously, the aqueous or water-containing suspension of finely divided **riboflavin** is continuously sprayed into a fluidized bed composed of dry **riboflavin.** The spraying rate is adjusted so that the fluidized bed has a temperature appropriate for the required degree of drying. It is accordingly determined in the final analysis by the difference between the entry and exit temperatures of the fluidizing gas.

SUMM In the continuous process, finely divided **riboflavin** is used in the fluidized bed only on first starting up the drier. The dry product obtained thereafter has a virtually constant particle size ratio. A defined portion of this is continuously removed and

fractionated according to the particle size. The fraction in the particle size range from 50 to 450 μm is ejected as required product, and the fine particles and/or the fine particles obtained by milling larger particles are continuously returned to the fluidized bed to maintain the **granulation** process. In each case, the amount of **riboflavin** removed as required product is continuously sprayed into the fluidized bed in the form of the aqueous suspension of finely divided **riboflavin.**

SUMM The **riboflavin** suspension is introduced by means of the single-fluid hollow cone nozzle into a heated drying tower where it is dried and discharged at the lower end of the tower. The gas entering the drying tower is generally at from about 100 to 200, preferably 130° to 170° C., and the residence time is generally about 20 to 40 seconds. In order to obtain a non-dusting **vitamin B2** microgranule fraction it is necessary for the dried product from the drying tower to be subjected to a suitable separation. The discharge cone of the drying tower can be designed to carry out this separation, as described in German patent 33 44 509, for example. This separation results in the non-dusting microgranules being deposited as required fractions, while the smaller particles (<20 μm) leave the drying tower with the gas. This fine material is removed from the gas in downstream separators (cyclones, filters) and can be mixed with the dry aqueous **riboflavin** suspensions (recycling). The proportion of the dusting fine fraction depends on the solids content of the suspension delivered to the hollow cone nozzle and on the admission pressure thereat. The proportion of fines may be from about 5 to 40%. The proportion of fines to be recycled is only about 5 to 10% when the solids content of the discharge is about 25 to 30% and the admission pressure of the nozzle is about 15 bar.

SUMM It is also possible by disk-type spray drying of **riboflavin** suspensions, without addition of substantial amount of binders, to prepare microgranules which, after removal of the fines (<20 μm) as described above, have very good handling properties.

SUMM The spray **granules** or microgranules of **riboflavin** prepared in an industrially straight forward manner by the process according to the invention surprisingly have considerable advantages when used by comparison with commercial **riboflavin** products disclosed to date. They have particular advantages in applications where the presence of binders or **granulation** auxiliaries is unwanted.

DETD About 2.5 kg/h of an approximately 20% strength aqueous suspension of a very finely divided **riboflavin** (bulk density about 0.1 kg/l; **riboflavin** content 99.5%; pharmaceutical product) at 20° C. were continuously sprayed through a two-fluid nozzle into a fluidized bed of **riboflavin** of approximately the same composition. The fluidizing gas entered at 170° C. The amount sprayed in was set so that the fluidized bed was at 71° to 72° C.

DETD About 0.5 kg/h of the required **riboflavin** spray **granules** (particle size range 125 to 250 μm) was obtained.

DETD 2.5 kg/h of an approximately 20% strength aqueous suspension of a very finely divided commercial **riboflavin** (bulk density about 0.1 kg/l; **riboflavin** content 96%; animal feed quality) were sprayed into a **riboflavin** fluidized bed. The fluidizing gas entered at 160° to 170° C. The amount sprayed in was set so that the fluidized bed was at 78° to 80° C.

DETD About 0.5 kg/h of **riboflavin** spray **granules** with the required particle size range from 125 to 250 μm was obtained as in Example 1.

CLM What is claimed is:

1. A process for preparing spray **granules** having a particle size range from about 50 to 450 μm which contain no binder, are non-dusting and free-flowing, from finely divided **riboflavin** having a purity of 98 to 100%, an average maximum particle diameter of about 0.1 to 50 μm and a bulk density of less than 0.2 g/ml, which comprises: subjecting an aqueous binder-free suspension containing from 5 to 30% by weight of said finely divided **riboflavin** to fluidized bed spray drying at a temperature of from 20° to 100° C.

2. The process of claim 1, wherein the average maximum particle diameter of the finely divided **riboflavin** is from about 10 to 30 μm.

3. A process as defined in claim 1, wherein pure **riboflavin** obtained by rapid precipitation from acidified aqueous **riboflavin** solutions at below about 50° C. is used as said finely divided **riboflavin.**

4. A process as defined in claim 1, wherein pure **riboflavin** obtained by rapid precipitation and rapid cooling of hot aqueous **riboflavin** solutions at a pH of from 0.8 to 6.5 is used as said finely divided **riboflavin.**

5. A process as defined in claim 1, wherein pure **riboflavin** obtained in the purification of crude **riboflavin** by the method of by slow precipitation of **riboflavin** from acidic aqueous solutions at from 90° to 100° C. followed by reprecipitation as defined in claim 3 is used as said finely divided **riboflavin.**

6. A process as defined in claim 1, wherein pure **riboflavin** obtained in the purification of crude **riboflavin** by the method of by slow precipitation of **riboflavin** from acidic aqueous solutions at from 90° to 100° C. followed by reprecipitation as defined in claim 4 is used as said finely divided **riboflavin.**

7. A process as defined in claim 1, wherein pure **riboflavin** obtained in the purification of crude **riboflavin** by the method of by slow precipitation of **riboflavin** from acidic aqueous solutions at from 90° to 100° C. followed by wet milling in a colloid mill is used as said finely divided **riboflavin.**

8. The process of claim 1, wherein the fluidized bed spray drying is carried out by a) introducing pure, finely divided **riboflavin** having an average maximum particle diameter of about 0.1 to 50 μm in dry form into a fluidized bed drier in which the bed is kept at from 20° to 100° C., b) adding to this fluidized **riboflavin** bed the aqueous suspension of the pure finely divided **riboflavin** defined in claim 10 in sprayed form in accordance with the rate of drying, c) maintaining the finely divided **riboflavin** defined in claim 10 in the fluidized bed until a substantial amount of the **riboflavin** has a particle size of from 50 to 450 μm, drawing off the **riboflavin** particles from the fluidized bed and separating them into fractions based on size,

d) ejecting the fraction with the particle size range from about 50 to 450 μm, and e) returning the particles having a particle size finer than 50 μm and/or the fine particles obtained by milling the particles having a particle size larger than 450 μm to the **granulation** process.

9. The process of claim 8, wherein the fluidized bed spray drying is carried out continuously in a fluidized bed which is composed of spray **granules** or microgranules of pure **riboflavin** and is kept at from 50° to 90° C., and wherein a suitable portion of the resulting dry product is continuously removed from the fluidized bed and separated into particle fractions based on size.

10. The process of claim 9, wherein the fluidized bed of spray **granules** or microgranules is kept at from 60° to 80° C.

IT **83-88-5P, Riboflavin**, preparation
(preparation of, with improved workability properties, method for)

L103 ANSWER 14 OF 15 USPATFULL on STN
ACCESSION NUMBER: 92:100915 USPATFULL Full-text
TITLE: Removal of **riboflavin** from fermentation suspensions
INVENTOR(S): Faust, Tillmann, Weisenheim, Germany, Federal Republic of
Meyer, Joachim, Hessheim, Germany, Federal Republic of
Wellinghoff, Georg, Mannheim, Germany, Federal Republic of
Gosele, Walter, Heidelberg, Germany, Federal Republic of
Martin, Christoph, Mannheim, Germany, Federal Republic of
Grimmer, Johannes, Ludwigshafen, Germany, Federal Republic of
PATENT ASSIGNEE(S): BASF Aktiengesellschaft, Ludwigshafen, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5169759		19921208	
APPLICATION INFO.:	US 1991-644609		19910123	(7)

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1990-4002066	19900125

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Naff, David M.
ASSISTANT EXAMINER: Lankford, L. Blaine
LEGAL REPRESENTATIVE: Keil & Weinkauf
NUMBER OF CLAIMS: 8
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT: 293
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB **Riboflavin** is removed from fermentation suspensions by them being heated at from 50° to 90° C. for from 1 to 3 hours, than cooled to from 0° to 30° C. over a period of from 1 to 5 hours, and subsequently being centrifuged to

give a sediment fraction and liquid fraction in such a way that the sediment fraction contains predominantly **riboflavin** crystals as solid, and the liquid fraction contains virtually no crystalline **riboflavin**, and, where appropriate, resuspending the sediment fraction in from 0.5 to 2 parts by volume of water per part by volume of sediment fraction and repeating procedure c.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Removal of **riboflavin** from fermentation suspensions

IN **Martin, Christoph**, Mannheim, Germany, Federal Republic of

AB **Riboflavin** is removed from fermentation suspensions by them being heated at from 50° to 90° C. for from 1 to 3 hours, than cooled to from 0° to 30° C. over a period of from 1 to 5 hours, and subsequently being centrifuged to give a sediment fraction and liquid fraction in such a way that the sediment fraction contains predominantly **riboflavin** crystals as solid, and the liquid fraction contains virtually no crystalline **riboflavin**, and, where appropriate, resuspending the sediment fraction in from 0.5 to 2 parts by volume of water per part by volume of sediment fraction and repeating procedure c.

SUMM The present invention relates to an improved process for removing **riboflavin** from fermentation suspensions by centrifugation.

SUMM DE-C 2 920 592 discloses a process for removing **riboflavin** from fermenter suspensions in which the fermentation suspensions are diluted with from 25 to 100% by volume of water and subsequently heated at from 50° to 65° C. for from 15 to 45 minutes. After the suspensions have been cooled they are centrifuged twice to concentrate the **riboflavin**. The consequence of the dilution is that a larger volume of fermenter suspension has to be processed, which increases the costs of processing and the losses of **riboflavin** owing to some dissolving in the added water.

SUMM It is an object of the present invention to remove **riboflavin** from fermenter suspensions with minimal loss of **riboflavin** to give a solid with a maximum **riboflavin** content.

SUMM We have found that this object is achieved by a process for removing **riboflavin** from fermentation suspensions by centrifugation, which comprises

SUMM c) being centrifuged to give a sediment fraction and a liquid fraction in such a way that the sediment fraction contains mainly **riboflavin** crystals as solid, and the liquid fraction contains virtually no crystalline **riboflavin**,

SUMM The **riboflavin** fermentation suspensions can be obtained by conventional processes (see, for example, EP-A 231 605, EP-A 211 289; T. Szczesniak et al., Acta Microbiologica Polonica Ser. B, 3 (1971) 29-34 and 91-95), for example using mutants of yeast cells of the genus Saccharomyces, mutants of the strains Candida flareri GA 18Y8-6#2 and 6A 18Y8-6#2#11 and mutants of the strain Ashbya gossypii.

SUMM These fermentation suspensions contain up to 20% by weight of **riboflavin** based on the total solids content of the suspensions. The remaining solids are essentially composed of complex cellular constituents.

SUMM It is essential for the process according to the invention that the fermenter suspension is heated, preferably for from 1 to 3 hours, in

particular for from 1 to 2 hours. This brings about a transformation in the **riboflavin** crystals in which predominantly larger crystals are formed at the expense of smaller ones.

SUMM The fermentation suspension is cooled to from 0° to 30° C. preferably over a period of from 1 to 8 hours, in particular 1 to 5 hours. This achieves a further optimization in the form of the **riboflavin** crystals.

SUMM The characteristics of the **riboflavin** crystals produced in this way make it possible, when suitable equipment is used, to separate the crystals optimally from the complex constituents of the cells and the media, which have lower specific gravities, in the fermentation suspensions, i.e. to fractionate into a sediment fraction predominantly containing **riboflavin** crystals as solid and into a liquid fraction which contains virtually no crystalline **riboflavin** but does contain a large part of the complex cellular constituents.

SUMM Suitable equipment for removing **riboflavin** from the fermenter suspensions comprises decanter-type centrifuges which allow separation into two fractions when operated on the classification principle. Classification means the separation of a slurry only into a more or less dewatered cake and an overflow containing the fine sediments (cf. Winnacker, Richter, Chemische Technologie, 1984, volume 1, pages 73 et seq.).

DETD The geometry and the operation are optimized for the suspension of **riboflavin** crystals recrystallized according to the invention. The important parameters are the shape and speed of rotation of the bowl, the differential speed of rotation of the helical conveyor, the overflow height (6) and the suspension throughput, i.e. the surface loading.

DETD In order to compensate for variations in the **riboflavin** suspension with regard to solids content and the ratio of **riboflavin** to biomass and other constituents of the media in the suspension, the centrifuge ought to have the largest possible active classification area. This is achieved, on the one hand, by using a bowl (1) with a high slenderness ratio (slenderness ratio= length/diameter of the centrifuge), i.e. a slenderness ratio of from 3 to 6, preferably of 4 or above, and, on the other hand, by shiftingthe ratio of the cylindrical sedimentation part (3) to the conical dewatering part (4) in favor of the sedimentation part by designing the conical part with an angle of, advantageously, from 10° to 25°, especially from 10° to 17°.

DETD The overflow height (6) of the decanter must also be suited to the **riboflavin** crystal suspension. This preferably entails using an overflow diameter (7) which is about ±10 mm different from the sediment discharge diameter (8). If the selected height (6) is too great (when the overflow diameter< sediment discharge diameter), there may be a short circuit leading to emergence of feed suspension at the sediment discharge,which reduces product purity. If the height is too low (when the overflow diameter> sediment discharge diameter), piling up of solid in the dewatering part leads to increased losses in **riboflavin** in the overflow.

DETD In order to achieve an optimal classification between the **riboflavin** crystals on the one hand and the cell material and the constituents of themedia on the other hand, i.e. to have an optimal residence time in the decanter, it is necessary to match the speed of rotation of the bowl, the differential speed of rotation of the helical conveyor and the suspension throughput for a given decanter size. For

example, if the selected speed of rotation of the bowl is too low at a given suspension throughput, the insufficient centrifugal force results in an increased loss of **riboflavin** crystals in the overflow. On the other hand, if the selected speed of rotation is too high, the increased sedimentation of cell material and constituents of the media results in a smaller improvement in product purity.

DETD Hence the present invention also relates to a process, as defined above, for removing **riboflavin** from fermentation suspensions, which comprises thefermentation suspension being centrifuged in step c) to give a sediment fraction and a liquid fraction so that at least 60% of the solids in the sediment fraction is composed of **riboflavin** crystals, and the liquid fraction still contains a large part of the complex cellular constituents.This can advantageously be achieved by carrying out the centrifugation in step c) in a decanting centrifuge operated by the classification principle. It is particularly advantageous for the centrifugation in step c) to be carried out in a decanter-type centrifuge with full casing and a helical conveyor and with a slenderness ratio of 4 or greater and a conical part with an angle of from 10° to 25°, and operatingit on the classification principle, with the overflow diameter being equal to the sediment discharge diameter ±10 mm.

DETD The solid in the sediment fraction is more than 60% by weight **riboflavin.** It is possible to resuspend and recentrifuge the sediment fraction to increase the proportion of **riboflavin** in the total solids content further.

DETD The sediment fractions containing more than 60% by weight of **riboflavin** canbe employed directly after the dewatering as animal feed additives or, after further purification, for pharmaceutical purposes.

DETD The sediment fraction can be dried, for example, by fluidized bed spray **granulation.**

DETD The process according to the invention can be used to obtain in a straightforward manner and with low **riboflavin** losses from fermentation suspensions up to about 60% pure **riboflavin** with a single decantation and about 75 to 88% pure **riboflavin** with repetition of the decanting procedure.

DETD A fermentation suspension which was composed of about 85% by weight water and 15% by weight solid which contained about 17% by weight **riboflavin** washeated at 60° C. for two hours (h). The fermentation suspension was then cooled to 20° C. over the course of 5 hours. The suspension treated in this way was centrifuged in a centrifuge with full casing and ahelical conveyor and with a slenderness ratio of 4, a conical part with an angle of 17°, an overflow diameter of 3 mm less than the sediment discharge diameter, a suspension feed approximately at the junction of thecylindrical and conical parts of the centrifuge and a surface loading of 1.3 l/(m.sup.2 .multidot.h) in such a way that the sediment fraction was composed of 20% by weight solid and 80% by weight water.

DETD The solid in the sediment fraction contained 63% by weight **riboflavin**, and the **riboflavin** losses were 1.8% by weight.

DETD The resulting sediment fraction was composed of 66% by weight **riboflavin**, and the **riboflavin** losses were 1.9% by weight.

DETD The sediment fraction obtained as in Example 1 was diluted with 0.8 part byvolume of water per part by volume of sediment fraction and, for further concentration, centrifuged in a centrifuge with full casing and a helical conveyor and with a slenderness ratio of about 4, a conical part with an angle of 17°, equal overflow and sediment discharge diameters, a suspension feed approximately at the junction of the

cylindrical sedimentation part with the conical dewatering part and with a surface loading of 0.5 l/(m.sup.2 .multidot.h). The differential speed of rotationwas adjusted to the rate of feed so that piling up of solid was thus prevented. The solid in the resulting sediment fraction contained 88% by weight **riboflavin** with the **riboflavin** losses being 1.0% of the crystal suspension employed in Example 1.

DETD This was followed by concentration in a centrifuge with full casing and with a slenderness ratio of about 3, a conical part with an angle of 10°, a dry section of 115 mm caused by difference of 20 mm between the overflow and sediment discharge diameters), a suspension feed approximately at the cylindrical/conical junction and a surface loading of0.8 l/(m.sup.2 .multidot.h). The solid in the resulting sediment fraction contained 46% by weight of **riboflavin**, and the **riboflavin** losses were 6.5%of the initial suspension.

DETD The solid in the resulting sediment fraction contained 58% by weight **riboflavin**, and the **riboflavin** losses were 4.4%.

CLM What is claimed is:

1. A process for removing **riboflavin** from fermentation suspensions by centrifugation, which consists essentially of: a) heating the fermentation suspension at from 50° to 90° C. for from 1 to 3 hours; b) cooling the suspension to from 0° to 30° C. over a period of from 1 to 10 hours, and thereafter, c) centrifuging the suspension in a decanting centrifuge operated by the classification principle whereby a sediment fraction is formed which contains at least 60% by weight of solid **riboflavin** crystals and a liquid fraction is formed which contains essentially no crystalline **riboflavin** but does contain a large part of the complex cellular constituents of the suspension, whereby undesirable dilution with water of the fermentation suspension is not required.

2. The process of claim 1, wherein the sediment fraction from (c) is resuspended in from 0.5 to 2 parts by volume of water per part by volume of sediment fraction and the new suspension is subjected one or more times to the centrifuging procedure of (c), whereby a sediment fraction is formed containing from 75 to 88% by weight of pure **riboflavin**

.

6. A process for removing **riboflavin** from fermentation suspensions defined in claim 1, wherein the centrifugation in step c) is carried out in a decanting centrifuge which has a full casing and a helical conveyor and has a slenderness ratio of 4 or greater and a conical part with an angle of from 10° to 25°, and which is operated by the classification principle with the overflow diameter being equal to the sediment discharge diameter ±10 mm.

7. A process for removing **riboflavin** from fermentation suspensions as defined in claim 1, wherein the centrifugation in step c) is carried out in a decanting centrifuge with full casing and a helical conveyor and with a slenderness ratio of 4 or greater and a conical part with an angle of from 10° to 25°, and it is operated by the classification principle with the differential speed of rotation of the helical conveyor being from ±0.1 to ±1% of the speed of rotation of the bowl and the surface loading being from 0.8 to 1.8 l/(m.sup.2 .multidot.h) for the first decantation and from 0.2 to 0.8 l/(m.sup.2 .multidot.h) if the decantation is repeated.

8. A process for removing **riboflavin** from fermentation suspensions as defined in claim 7, wherein the surface loading is from 1 to 1.5 l/(m.sup.2 .multidot.h) in the first decantation and from 0.4 to 0.6 l/(m.sup.2 .multidot.h) if the decantation is repeated.

IT Temperature effects, biological
(in **riboflavin** purification from fermentation broths)
IT Fermentation
(**riboflavin**, heat treatment in relation to)
IT **83-88-5P**, **Riboflavin**, biological studies
(purification from fermentation broth of, heat treatment in)

L103 ANSWER 15 OF 15 USPATFULL on STN

ACCESSION NUMBER:	90:95123 USPATFULL Full-text
TITLE:	Preparation of **riboflavin**, produced by a microbial method, in the form of spray-dried **granules** or microgranules
INVENTOR(S):	Meyer, Joachim, Hessheim, Germany, Federal Republic of Buehler, Wolfgang, Hockenheim, Germany, Federal Republic of Grimmer, Johannes, Ludwigshafen, Germany, Federal Republic of Eipper, Gunter, Ludwigshafen, Germany, Federal Republic of Kiefer, Hans, Wachenheim, Germany, Federal Republic of **Martin, Christoph**, Mannheim, Germany, Federal Republic of
PATENT ASSIGNEE(S):	BASF Aktiengesellschaft, Ludwigshafen, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4977190		19901211	
APPLICATION INFO.:	US 1989-363853		19890609	(7)

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1988-3819745	19880610

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Shah, Mukund J.
ASSISTANT EXAMINER:	Cseh, C. L.
LEGAL REPRESENTATIVE:	Oblon, Spivak, McClelland, Maier & Neustadt
NUMBER OF CLAIMS:	5
EXEMPLARY CLAIM:	1
LINE COUNT:	352

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB **Riboflavin** produced by a microbial method is prepared in the form of free-flowing, non-dusting, spray-dried **granules** or microgranules as a feed additive by removing water from the mixture discharged from microbial fermentation for the preparation of **riboflavin**, wherein the mixture is subjected to

(a) a fluidized-bed spray-drying process

(b) a one-material spray-drying process or

(c) a disk spray-drying process without significant amounts of binders being added to the discharged fermentation mixture.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Preparation of **riboflavin**, produced by a microbial method, in the form of spray-dried **granules** or microgranules

IN **Martin, Christoph**, Mannheim, Germany, Federal Republic of

AB **Riboflavin** produced by a microbial method is prepared in the form of free-flowing, non-dusting, spray-dried **granules** or microgranules as a feed additive by removing water from the mixture discharged from microbial fermentation for the preparation of **riboflavin**, wherein the mixture is subjected to

SUMM The present invention relates to a process for the preparation of **riboflavin**, produced by a microbial method, in the form of spray-dried **granules** or microgranules as a feed additive by removing water from the mixture discharged from microbial fermentation by a spray-drying method.

SUMM The preparation of **riboflavin** by microbial fermentation processes is disclosed in, for example, EP-A-231 605, EP-A-211 289 and German Laid-Open Application DOS 3,420,310. The **riboflavin** produced industrially by this method serves as a feed additive. The end product of the production of **riboflavin** by fermentation is generally isolated together with the biomass in the form of a **riboflavin** concentrate by evaporating down the resulting culture liquid. Unfortunately, the products obtained in this manner have serious disadvantages in some cases. For example, they have poor flow, which in practice, owing to bridge formation, may result in storage silos being emptied insufficiently, if at all, and hence in the accuracy of metering being adversely affected. Furthermore, they have only a low bulk density. This leads in practice to high packaging, storage and transport costs. In particular, however, the known products give rise to large amounts of dust and become charged, resulting in handling difficulties during mixing to give premixes and feeds. Spray-drying of the fermentation product by means of a two-material nozzle is also known, but the spray-dried products obtained by this method also do not completely meet all requirements with regard to performance characteristics. For example, when mixed into water for the preparation of liquid feed, they tend to form lumps. The lumps formed are difficult to break up again.

SUMM It is an object of the present invention to provide a formulation process for **riboflavin** produced by microbial fermentation, which process gives free-flowing, non-dusting spray-dried **granules** or microgranules which do not have the difficulties described during preparation of premixes or feeds.

SUMM We have found that this object is achieved and that, surprisingly, free-flowing, non-dusting **riboflavin**-containing spray-dried **granules** or microgranules which are easy to handle are obtained if the mixture discharged from microbial fermentation is spray-dried in a very particular manner, even without the addition of binders.

SUMM The present invention accordingly relates to a process for the preparation of **riboflavin**, produced by a microbial method, in the form of free-flowing, nondusting, spray-dried **granules** and microgranules as a feed additive by removing water from the mixture discharged from microbial fermentation for the preparation of **riboflavin**, wherein the mixture discharged from the fermentation is subjected to

SUMM Surprisingly, **riboflavin granules** prepared in this manner have advantages, in some cases considerable ones, over the known

and commercial products with regard to performance characteristics.

SUMM For the preparation of spray-dried **granules** or microgranules, the fermentation broth obtained in the preparation of **riboflavin** by fermentation can be used as such or in concentrated from. The fermentation broth is understood as being the mixture discharged from a fermentation, which can be carried out in a known manner (cf. EP-A 211 289, EP-A 231 605, German Laid-Open Application DOC 3,420,310 or Genevieve C. Barrerc in Biochemistry and Genetics of Vitamin Production, Nato Advanced Study Institute Series, Series A, 87 (1985), 141-169, in particular 150-158). The medium for the fermentation contains carbon sources, such as carbohydrates, organic acids, alcohols or fats, and nitrogen sources, such as protein-containing meals, peptones, amino acids, urea or inorganic nitrogen salts. Sulfates, phosphates, carbonates or nitrates of magnesium, potassium, sodium, calcium or manganese and even vitamins may also be used in the fermentation medium.

SUMM The concentration of **riboflavin** in the fermentation broth can be increased by filtration or centrifuging and decanting (cf. DE 29 20 592).

SUMM In contrast to the known spray-drying of the mixture discharged from the fermentation, in which this mixture is usually sprayed into a drying tower by means of a two-material nozzle, in the fluidized-bed spray-drying process used according to the invention the suspension is sprayed continuously or batchwise into a fluidized bed of dry reaction product. The drying means is provided with suitable apparatuses which make it possible to obtain a certain particle size fraction and to maintain the **granulation** process (cf. K. Kroll Trocknungstechnik, Volume II Trockner und Trocknungsverfahren, 2nd Edition, Springer-Verlang, Berlin, 1978, pages 221-223).

SUMM (a) **riboflavin** in the form of a dry powder, spray-dried **granules** or microgranules is initially taken in a fluidized-bed drier in a fluidized bed kept at 20°-150° C., preferably 50°-100° C.,

SUMM (b) the fermentation mixture obtained is added in atomized form, if necessary after concentration of **riboflavin** by decantation, at the rate at which drying takes place,

SUMM (c) the **riboflavin** particles are removed from the fluidized bed after a suitable residence time and separated into particle fractions by a suitable apparatus,

SUMM (e) the finer particles and/or the fine particles obtained by milling of larger particles are recycled to the **granulation** process.

SUMM To carry out the process, it is first necessary to convert dry **riboflavin** powder corresponding to the prior art into a **riboflavin** product with which a fluidized bed can be produced. In the batchwise process, a relatively finely divided product can be initially taken in the fluidized bed. Depending on the residence time of the particles in the fluidized-bed drier, a dry product having a smaller or larger particle size range is then obtained. Particles in the size range of about 100 to 250 μm have the desired handling properties and are therefore recovered as the desired product. Smaller particles and **riboflavin** product obtained by suitable milling of larger particles are used as fluidized bed material for further batches.

SUMM To carry out the continuous process, the mixture discharged from the fermentation is sprayed continuously, preferably after concentration of **riboflavin** by decantation, into a fluidized bed consisting of a dry **riboflavin** product. The spraying speed is adjusted so that the fluidized bed is at a temperature corresponding to the desired degree of drying. Accordingly, this is finally determined from the difference between the inlet temperature and outlet temperature of the fluidizing gas.

SUMM In the continuous process, finely divided **riboflavin** is used as a starting material only when the fluidized-bed drier is started up for the first time. Thereafter, a dry product of virtually constant particle size ratio is obtained. A certain part of this product is removed continuously and separated into particle size fractions. The fraction having a particle size of from 100 to 250 μm is separated off as the desired product, and the fine particles and/or the fine particles obtained by milling of larger particles are recycled continuously to the fluidized bed to maintain the **granulation** process. In each case, roughly the amount of **riboflavin** removed as the desired product is sprayed continuously into the fluidized bed, in the form of the discharged fermentation mixture to be dried.

SUMM The **riboflavin** spray-dried **granules** or microgranule prepared by the novel process surprisingly have considerable advantages over the conventional and commercial dry powders with regard to performance characteristics.

DETD In a fluidized-bed drier, from 0.9 to 1 kg/hour of an aqueous suspension (fermenter discharge concentrated by decantation), consisting of 78 parts of water and 22 parts of solids (containing 73.1% of **riboflavin** according to HPLC) and at 20° C., was sprayed continuously by means of a two-material nozzle into a fluidized bed consisting of 96% strength **riboflavin** having a mean particle size of 0.12 mm. The fluidizing gas had an inlet temperature of from 140° to 150° C. The amount sprayed in was such that the resulting temperature of the fluidized bed was from 75° to 80° C. The initially taken fluidized bed was changed five times in the course of about 25 hours and the product formed was removed. After this time, the initially taken **riboflavin** had been virtually completely removed from the drying process, and the product contained in the fluidized bed was composed of 73.1% of **riboflavin** and 26.9% of biomass and had the particle size distribution described below. A part of the initially taken fluidized bed was removed continuously and was separated into 3 particle fractions by screening means. This gave

DETD In a fluidized-bed drier, from 0.75 to 0.8 kg/h of an aqueous suspension (fermenter discharge concentrated by decantation), consisting of about 80.3% of water and 19.7% of solids (containing about 63.9% of **riboflavin** according to HPLC) and at 20° C., was sprayed continuously by means of a two-material nozzle into a fluidized bed consisting of **riboflavin** having roughly the same composition. The fluidizing gas had an inlet temperature of from 140° to 150° C. The amount sprayed in was such that the resulting temperature of the fluidized bed was about 75° C.

DETD About 0.15 kg of spray-dried **riboflavin granules** per h was obtained.

DETD In the Table below, the essential performance characteristics of the **riboflavin** product obtained in Examples 1 and 2 are compared with those of conventional commercial products.

DETD

Performance characteristics

	Flow behavior		Dust test				
	Flow angle	Flow	Mean par-ticle size	Par-ticles	Bulk density		
	[degrees]	[mm] sec]	[mm]	[mio/g]	[g/cm.sup.3]	Color	Odor
Riboflavin [prepared according to Example]	30	4 5/3/1	0.21	0.21	0.55	Yellowish brown	Slight odor of yeast
Example 2	32	4 5/2/1	0.14	0.70	0.49	Yellowish brown	Slight oder of yeast
Riboflavin feed* 62% strength (BASF)	55	24 60/22/15	0.04	29.9	0.32	Yellow	Intense odor of fermenter residue
Riboflavin feed* 80% (Hoffmann-La Roche)	31	5 24/14/8	0.06	8.8	0.41	Orange-brown	Slightly musty

*Prepared by spraydrying using a twomaterial nozzle

DETD In a fluidized-bed drier, about 100 kg/h of a fermenter discharge concentrated by decanting, consisting of 76% of water and 24% of solids (containing 70.8% of **riboflavin**) and at 20° C., were sprayed continuously by means of a two-material nozzle into a fluidized bed consisting of **riboflavin** having roughly the same composition. The inlet temperature of the fluidizing gas was 170° C. The amount sprayed in was such that the resulting temperature of the fluidized bed was from 71° to 72° C.

DETD About 24.5 kg/h of the desired spray-dried **riboflavin granules** (particle size of from 100 to 250 μm) were obtained.

DETD In a fluidized-bed drier, 0.95 kg/h of a fermenter discharge which was not concentrated and consisted of 86% of water and 14% of solids were sprayed into a fluidized bed of **riboflavin**. The fluidizing gas had an inlet temperature of from 160 ° to 170° C. The amount sprayed in was such that the resulting temperature of the fluidized bed was from 78° to 80° C.

DETD From 0.1 to 0.12 kg/h of spray-dried **riboflavin granules** having the desired particle size of from 100 to 250 µm was obtained similarly to Example 1.

CLM What is claimed is:

1. A process for preparation of **riboflavin**, produced by a microbial method, in the form of free-flowing, non-dusting, spray-dried **granules** or microgranules, comprising removing water from the mixture discharged from a microbial fermentation for the preparation of **riboflavin**, wherein the mixture discharged from the fermentation is subjected to a drying process selected from the group consisting of a fluidized-bed spray-drying process, a one-material spray-drying process, and a disk spray-drying process, in the absence of significant amounts of binders being added to the mixture discharged from the fermentation.

2. A process as claimed in claim 1, wherein said drying process is fluidized-bed spray-drying process and wherein (i) **riboflavin** in the form of a dry powder, spray-dried **granules** or microgranules is used in a fluidized-bed drier as a fluidized bed at 20°-150° C.; (ii) said mixture discharged from the fermentation is added in atomized form to said fluidized-bed drier at the rate at which drying takes place, to produced **riboflavin** particles; (iii) said **riboflavin** particles are removed from the fluidized bed after a residence time sufficient to form particles having a particle size of from about 100 to 250 µm and separated into particle fractions; (iv) the particle fraction having a particle size of from about 100 to 250 µm is removed; and (v) the particles having a particle size finer than 100 µm and/or fine particles obtained by milling of larger particles are recycled to the **granulation** process.

3. A process as claimed in claim 2, wherein, to carry out the fluidized-bed spray drying by continuous procedure, a fluidized bed kept at from 50° to 100° C. and consisting of **riboflavin** spray-dried **granules** or microgranules is used, a part of the resulting dried product is removed continuously from the initially taken fluidized bed and is separated into particle fractions, the particle fraction having a particle size of about 100-250 µm is separated off as the desired product and the fine particles and/or the fine particles obtained by milling of larger particles are recycled to the fluidized bed in order to maintain the **granulation** process.

4. A process as claimed in claim 3, wherein a fluidized bed kept at from 60° to 80° C. and consisting of **riboflavin** spray-dried **granules** or microgranules is used.

IT Drying
(**riboflavin** preparation **granulation** by, from fermentation medium)

IT **83-88-5P, Riboflavin**, preparation
(manufacture of **granulated**, by drying of fermentation broth)

TEXT SEARCH

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=> => fil medline drugb agricola pascal frosti caba biotechno biosis biotechds
esbio lifesci fsta toxcenter bioeng ceaba embase dpci scisearch
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=> d que l96; d que l98; d que l100; d que l101
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L88       26733 SEA L2
L90       33382 SEA MODIF?(2A)(B OR C OR BC)
L96          11 SEA L88 AND L90


L89       51821 SEA RIBOFLAVIN OR RIBO FLAVIN OR VITAMIN B2 OR VITAMINB2
L90       33382 SEA MODIF?(2A)(B OR C OR BC)
L94     1406599 SEA GRANUL?
L97          35 SEA L89 AND L90
L98           5 SEA L97 AND L94


L89       51821 SEA RIBOFLAVIN OR RIBO FLAVIN OR VITAMIN B2 OR VITAMINB2
L90       33382 SEA MODIF?(2A)(B OR C OR BC)
L91       77692 SEA FLUIDI?(W) BED#
L92      674348 SEA PRECIPITAT?
L93       25900 SEA (ACID#(2A)(MINERAL OR INORG?))
L97          35 SEA L89 AND L90
L100          3 SEA L97 AND (L91 OR L92 OR L93)


L89       51821 SEA RIBOFLAVIN OR RIBO FLAVIN OR VITAMIN B2 OR VITAMINB2
L90       33382 SEA MODIF?(2A)(B OR C OR BC)
L97          35 SEA L89 AND L90
L101          6 SEA L97 AND (PREP? OR MANUF?)


=> s l96,l98,l100,l101

  15 FILES SEARCHED...
L104         18 (L96 OR L98 OR L100 OR L101)

=> s l104 not l95

L105         17 L104 NOT L95

=> fil wpix; d que l47; d que l49; d que l52; d que l57

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http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<
'BI ABEX' IS DEFAULT SEARCH FIELD FOR 'WPIX' FILE

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L31          3154 SEA FILE=WPIX ABB=ON  RIBOFLAVIN#/BI,ABEX OR RIBO FLAVIN#/BI,AB
                  EX OR VITAMIN B2/BI,ABEX
L36        323133 SEA FILE=WPIX ABB=ON  MODIF?/BI,ABEX
L37          5865 SEA FILE=WPIX ABB=ON  L36(2A)B/BI,ABEX
L38          4314 SEA FILE=WPIX ABB=ON  L36(2A)C/BI,ABEX
L39             5 SEA FILE=WPIX ABB=ON  L36(2A)BC/BI,ABEX
L40             2 SEA FILE=WPIX ABB=ON  (RIBOFLAVIN/CN OR "RIBOFLAVIN HYDROCHLORI
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L41          1923 SEA FILE=WPIX ABB=ON  L40/DCR
L42          1924 SEA FILE=WPIX ABB=ON  (0503/DRN,DCN,DCRE OR R00503/DRN,DCN,DCRE
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L45          1511 SEA FILE=WPIX ABB=ON  B03-C/MC OR C03-C/MC
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B03-C B2 (RIBOFLAVIN)
C03-C B2 (RIBOFLAVIN)

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L47             8 SEA FILE=WPIX ABB=ON  (L31 OR L41 OR L42 OR L45) AND (L37 OR
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L31          3154 SEA FILE=WPIX ABB=ON  RIBOFLAVIN#/BI,ABEX OR RIBO FLAVIN#/BI,AB
                  EX OR VITAMIN B2/BI,ABEX
L32        153807 SEA FILE=WPIX ABB=ON  GRANUL?/BI,ABEX
L33          6414 SEA FILE=WPIX ABB=ON  FLUIDIZED BED#/BI,ABEX
L34        139368 SEA FILE=WPIX ABB=ON  PRECIPITAT?/BI,ABEX
L35         32098 SEA FILE=WPIX ABB=ON  ACID#/BI,ABEX(2A)(MINERAL/BI,ABEX OR
                  INORG?/BI,ABEX)
L40             2 SEA FILE=WPIX ABB=ON  (RIBOFLAVIN/CN OR "RIBOFLAVIN HYDROCHLORI
                  DE"/CN)
L41          1923 SEA FILE=WPIX ABB=ON  L40/DCR
L42          1924 SEA FILE=WPIX ABB=ON  (0503/DRN,DCN,DCRE OR R00503/DRN,DCN,DCRE
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                  DRN,DCN,DCRE OR 105627-0-1-0/DRN,DCN,DCRE)
L44         15081 SEA FILE=WPIX ABB=ON  FLUIDISED BED#/BI,ABEX
L45          1511 SEA FILE=WPIX ABB=ON  B03-C/MC OR C03-C/MC
L46          7193 SEA FILE=WPIX ABB=ON  B12-M11D/MC OR C12-M11D/MC
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B12-M11D PELLET, PRILL, GRANULE
C12-M11D PELLET, PRILL, GRANULE

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L49          2 SEA FILE=WPIX ABB=ON  (L31 OR L41 OR L42 OR L45) AND (L32 OR
               L46) AND (L33 OR L44) AND (L34 OR L35)



L31       3154 SEA FILE=WPIX ABB=ON  RIBOFLAVIN#/BI,ABEX OR RIBO FLAVIN#/BI,AB
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L32     153807 SEA FILE=WPIX ABB=ON  GRANUL?/BI,ABEX
L34     139368 SEA FILE=WPIX ABB=ON  PRECIPITAT?/BI,ABEX
L35      32098 SEA FILE=WPIX ABB=ON  ACID#/BI,ABEX(2A)(MINERAL/BI,ABEX OR
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L42       1924 SEA FILE=WPIX ABB=ON  (0503/DRN,DCN,DCRE OR R00503/DRN,DCN,DCRE
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L46       7193 SEA FILE=WPIX ABB=ON  B12-M11D/MC OR C12-M11D/MC
L52          3 SEA FILE=WPIX ABB=ON  (L31 OR L41 OR L42 OR L45) AND L34 AND
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L31       3154 SEA FILE=WPIX ABB=ON  RIBOFLAVIN#/BI,ABEX OR RIBO FLAVIN#/BI,AB
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L33       6414 SEA FILE=WPIX ABB=ON  FLUIDIZED BED#/BI,ABEX
L34     139368 SEA FILE=WPIX ABB=ON  PRECIPITAT?/BI,ABEX
L35      32098 SEA FILE=WPIX ABB=ON  ACID#/BI,ABEX(2A)(MINERAL/BI,ABEX OR
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L40          2 SEA FILE=WPIX ABB=ON  (RIBOFLAVIN/CN OR "RIBOFLAVIN HYDROCHLORI
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L41       1923 SEA FILE=WPIX ABB=ON  L40/DCR
L42       1924 SEA FILE=WPIX ABB=ON  (0503/DRN,DCN,DCRE OR R00503/DRN,DCN,DCRE
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               DRN,DCN,DCRE OR 105627-0-1-0/DRN,DCN,DCRE)
L44      15081 SEA FILE=WPIX ABB=ON  FLUIDISED BED#/BI,ABEX
L45       1511 SEA FILE=WPIX ABB=ON  B03-C/MC OR C03-C/MC
L57          2 SEA FILE=WPIX ABB=ON  (L31 OR L41 OR L42 OR L45) AND L34 AND
               L35 AND (L33 OR L44)


=> s l47,l49,l52,l57 not l43

L106        10 (L47 OR L49 OR L52 OR L57) NOT L43

=> fil uspatf; d que l72;d que l73; d que l81; d que l82

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HIGHEST GRANTED PATENT NUMBER: US7197769
HIGHEST APPLICATION PUBLICATION NUMBER: US2007067883
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REVISED CLASS FIELDS (/NCL) LAST RELOADED: Oct 2006
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Oct 2006
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L72            2 SEA FILE=USPATFULL ABB=ON  L67(L)L60


L59        42967 SEA FILE=USPATFULL ABB=ON  MODIF?(2A)(B OR C OR BC)
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L73            6 SEA FILE=USPATFULL ABB=ON  L66(2A)L59


L2             1 SEA FILE=REGISTRY ABB=ON  RIBOFLAVIN/CN
L58         1373 SEA FILE=USPATFULL ABB=ON  L2
L59        42967 SEA FILE=USPATFULL ABB=ON  MODIF?(2A)(B OR C OR BC)
L60          306 SEA FILE=USPATFULL ABB=ON  (MODIF?(2A)(B OR C OR BC))/IT
L61           43 SEA FILE=USPATFULL ABB=ON  L58 AND (L59 OR L60)
L69       274514 SEA FILE=USPATFULL ABB=ON  GRANUL?
L70         9334 SEA FILE=USPATFULL ABB=ON  GRANUL?/IT
L74        39711 SEA FILE=USPATFULL ABB=ON  FLUIDI? BED#
L75         3126 SEA FILE=USPATFULL ABB=ON  (FLUIDI? BED#)/IT
L76       396897 SEA FILE=USPATFULL ABB=ON  PRECIPITAT?
L77         1758 SEA FILE=USPATFULL ABB=ON  PRECIPITAT?/IT
L78         3140 SEA FILE=USPATFULL ABB=ON  (ACID#(L)(MINERAL OR INORG?))/IT
L79       136703 SEA FILE=USPATFULL ABB=ON  (ACID#(2A)(MINERAL OR INORG?))
L81            6 SEA FILE=USPATFULL ABB=ON  L61 AND (L69 OR L70) AND (L74 OR
                 L75 OR L76 OR L77 OR L78 OR L79)


L2             1 SEA FILE=REGISTRY ABB=ON  RIBOFLAVIN/CN
L58         1373 SEA FILE=USPATFULL ABB=ON  L2
L59        42967 SEA FILE=USPATFULL ABB=ON  MODIF?(2A)(B OR C OR BC)
L60          306 SEA FILE=USPATFULL ABB=ON  (MODIF?(2A)(B OR C OR BC))/IT
L61           43 SEA FILE=USPATFULL ABB=ON  L58 AND (L59 OR L60)
L74        39711 SEA FILE=USPATFULL ABB=ON  FLUIDI? BED#
L75         3126 SEA FILE=USPATFULL ABB=ON  (FLUIDI? BED#)/IT
L76       396897 SEA FILE=USPATFULL ABB=ON  PRECIPITAT?
L77         1758 SEA FILE=USPATFULL ABB=ON  PRECIPITAT?/IT
L78         3140 SEA FILE=USPATFULL ABB=ON  (ACID#(L)(MINERAL OR INORG?))/IT
L79       136703 SEA FILE=USPATFULL ABB=ON  (ACID#(2A)(MINERAL OR INORG?))
L82            6 SEA FILE=USPATFULL ABB=ON  L61 AND (((L74 OR L75) AND (L76 OR
                 L77 OR L78 OR L79)) OR ((L76 OR L77) AND (L78 OR L79)))


=> s l72,l73,l81,l82 not l71

L107          10 (L72 OR L73 OR L81 OR L82) NOT L71

=> fil capl; d que l14; d que l23; d que l24; d que l25;d que l26

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L8        19773 SEA FILE=CAPLUS ABB=ON  L2
L12       26078 SEA FILE=CAPLUS ABB=ON  GRANUL?/CW
L13       47732 SEA FILE=CAPLUS ABB=ON  FLUIDIZED BED#/OBI
L14           5 SEA FILE=CAPLUS ABB=ON  L8 AND L12 AND L13
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L17     1029830 SEA FILE=CAPLUS ABB=ON  MODIF?/BI
L18        5394 SEA FILE=CAPLUS ABB=ON  B/BI(2A)L17
L19        9231 SEA FILE=CAPLUS ABB=ON  C/BI(2A)L17
L20          51 SEA FILE=CAPLUS ABB=ON  BC/BI(2A)L17
L22        1555 SEA FILE=CAPLUS ABB=ON  L8(L)PREP/RL
L23           3 SEA FILE=CAPLUS ABB=ON  L22 AND (L18 OR L19 OR L20)
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L10      131793 SEA FILE=CAPLUS ABB=ON  GRANUL?/OBI
L13       47732 SEA FILE=CAPLUS ABB=ON  FLUIDIZED BED#/OBI
L15       26851 SEA FILE=CAPLUS ABB=ON  ACID#/OBI(L)(MINERAL/OBI OR INORG?/OBI)

L16      123048 SEA FILE=CAPLUS ABB=ON  PRECIPITAT?/OBI
L17     1029830 SEA FILE=CAPLUS ABB=ON  MODIF?/BI
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L19        9231 SEA FILE=CAPLUS ABB=ON  C/BI(2A)L17
L20          51 SEA FILE=CAPLUS ABB=ON  BC/BI(2A)L17
L21          19 SEA FILE=CAPLUS ABB=ON  L8 AND (L18 OR L19 OR L20)
L24           3 SEA FILE=CAPLUS ABB=ON  L21 AND (L10 OR L13 OR L15 OR L16)
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L8        19773 SEA FILE=CAPLUS ABB=ON  L2
L12       26078 SEA FILE=CAPLUS ABB=ON  GRANUL?/CW
L15       26851 SEA FILE=CAPLUS ABB=ON  ACID#/OBI(L)(MINERAL/OBI OR INORG?/OBI)
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L25             3 SEA FILE=CAPLUS ABB=ON  L8 AND L12 AND L15


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L8          19773 SEA FILE=CAPLUS ABB=ON  L2
L15         26851 SEA FILE=CAPLUS ABB=ON  ACID#/OBI(L)(MINERAL/OBI OR INORG?/OBI)

L16        123048 SEA FILE=CAPLUS ABB=ON  PRECIPITAT?/OBI
L26             3 SEA FILE=CAPLUS ABB=ON  L8 AND L15 AND L16


=> s l14,l23,l24,l25,l26 not l102

L108           11 (L14 OR L23 OR L24 OR L25 OR L26) NOT L102

=> dup rem l108,l105,l106,l107
DUPLICATE IS NOT AVAILABLE IN 'DPCI'.
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FILE 'AGRICOLA' ENTERED AT 10:33:41 ON 29 MAR 2007

FILE 'PASCAL' ENTERED AT 10:33:41 ON 29 MAR 2007
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FILE 'USPATFULL' ENTERED AT 10:33:41 ON 29 MAR 2007
CA INDEXING COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)
PROCESSING COMPLETED FOR L108
PROCESSING IS APPROXIMATELY 76% COMPLETE FOR L105
PROCESSING COMPLETED FOR L105
PROCESSING COMPLETED FOR L106
PROCESSING COMPLETED FOR L107
L109 39 DUP REM L108 L105 L106 L107 (9 DUPLICATES REMOVED)
ANSWERS '1-11' FROM FILE CAPLUS
ANSWER '12' FROM FILE MEDLINE
ANSWER '13' FROM FILE PASCAL
ANSWER '14' FROM FILE FROSTI
ANSWERS '15-16' FROM FILE CABA
ANSWERS '17-19' FROM FILE BIOSIS
ANSWER '20' FROM FILE TOXCENTER
ANSWER '21' FROM FILE DPCI
ANSWERS '22-30' FROM FILE WPIX
ANSWERS '31-39' FROM FILE USPATFULL

=> d abs ibib ed hitstr 1-11; d iall 12-21; d iall abeq tech 22-30; d ibib abs hit 31-39; fil hom

L109 ANSWER 1 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 3
AB Flowable, nondusty, binder-free riboflavin granulates (I) are prepared by subjecting an aqueous suspension of riboflavin crystals of crystal **modification B/C** to a fluidized bed spray drying process using a single fluid nozzle spray-drying process or a disk-type spray drying process. I tablet formulations are presented.

ACCESSION NUMBER: 2000:773961 CAPLUS Full-text
DOCUMENT NUMBER: 133:323292
TITLE: Spray-drying process for preparing spray **granules** containing flowable, nondusty, binder-free riboflavin
INVENTOR(S): Nowotny, Markus; Tritsch, Jean-Claude
PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.
SOURCE: Eur. Pat. Appl., 8 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1048668	A2	20001102	EP 2000-108560	20000419
EP 1048668	A3	20010328		
EP 1048668	B1	20030129		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6723346	B1	20040420	US 2000-550971	20000417
AT 231864	T	20030215	AT 2000-108560	20000419
ES 2189711	T3	20030716	ES 2000-108560	20000419
CA 2306502	A1	20001030	CA 2000-2306502	20000420
TW 253347	B	20060421	TW 2000-89107796	20000426
JP 2000327562	A	20001128	JP 2000-126926	20000427

IN 190891	A1	20030830	IN 2000-MA324		20000427
BR 2000002390	A	20001031	BR 2000-2390		20000428
NO 2000002283	A	20001031	NO 2000-2283		20000428
NO 318219	B1	20050221			
CN 1275375	A	20001206	CN 2000-118052		20000428
AU 770320	B2	20040219	AU 2000-30189		20000428
PRIORITY APPLN. INFO.:			EP 1999-108476	A	19990430

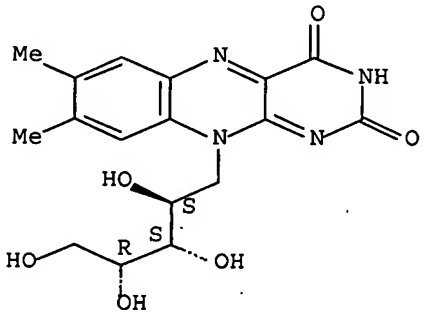
ED Entered STN: 05 Nov 2000

IT **83-88-5**, Riboflavin, processes
RL: FFD (Food or feed use); PEP (Physical, engineering or chemical process); PRP (Properties); BIOL (Biological study); PROC (Process); USES (Uses)
(spray-drying process for preparing spray **granules** containing flowable nondusty binder-free riboflavin of **B/C** crystal **modification**)

RN 83-88-5 CAPLUS

CN Riboflavin (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



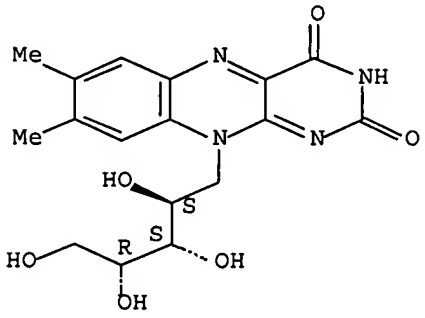
L109 ANSWER 2 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 4

AB Recombinant DNA engineering was combined with mutant selection and fermentation improvement to develop a strain of Bacillus subtilis that produces com. attractive levels of riboflavin. The B. subtilis riboflavin production strain contains multiple copies of a **modified B.** subtilis riboflavin biosynthetic operon (rib operon) integrated at two different sites in the B. subtilis chromosome. The modified rib operons are expressed constitutively from strong phage promoters located at the 5' end and in an internal region of the operon. The engineered strain also contains purine analog-resistant mutations designed to deregulate the purine pathway (GTP is the precursor for riboflavin), and a riboflavin analog-resistant mutation in ribC that deregulates the riboflavin biosynthetic pathway.

ACCESSION NUMBER:	1999:206110 CAPLUS Full-text
DOCUMENT NUMBER:	130:310705
TITLE:	Genetic engineering of Bacillus subtilis for the commercial production of riboflavin
AUTHOR(S):	Perkins, J. B.; Sloma, A.; Hermann, T.; Theriault, K.; Zachgo, E.; Erdenberger, T.; Hannett, N.; Chatterjee, N. P.; Williams, V, II; Rufo, G. A., Jr.; Hatch, R.; Pero, J.
CORPORATE SOURCE:	OmniGene Bioproducts, Cambridge, MA, 02138, USA
SOURCE:	Journal of Industrial Microbiology & Biotechnology (1999), 22(1), 8-18 CODEN: JIMBFL; ISSN: 1367-5435
PUBLISHER:	Stockton Press

DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 01 Apr 1999
IT **83-88-5P**, Riboflavin, preparation
RL: BMF (Bioindustrial manufacture); BIOL (Biological study); **PREP (Preparation)**
(genetic engineering of Bacillus subtilis for com. production of riboflavin)
RN 83-88-5 CAPLUS
CN Riboflavin (8CI, 9CI) (CA INDEX NAME)

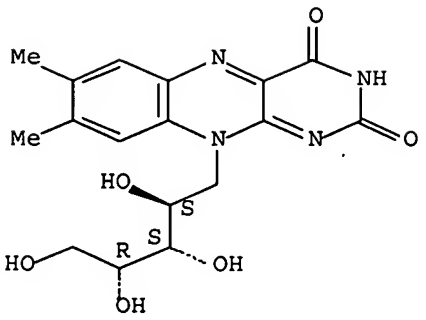
Absolute stereochemistry.



REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L109 ANSWER 3 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 5
AB The Hg vapors are effectively removed from vitamin B2 [83-88-5] manufacture waste gases in a new apparatus by chemical absorption with activated carbon. The method consists in filtering the Hg-containing waste gases through a layer of granular activated **C modified** with NaCl. The Hg vapors react with NaCl and O on the carbon surface to form readily retainable Hg compds. The spent sorbent is reused in metallic Hg manufacture The apparatus design is discussed.
ACCESSION NUMBER: 1982:90879 CAPLUS Full-text
DOCUMENT NUMBER: 96:90879
TITLE: Sanitary treatment of mercury vapors from vent discharges in the production of vitamin B2
AUTHOR(S): Fadeev, A. I.; Bushuev, V. P.; Zhdanov, E. V.
CORPORATE SOURCE: Nauchno-Issled. Inst. Ochistke Gazov, Dzerzhinsk, USSR
SOURCE: Promyshlennaya i Sanitarnaya Ochistka Gazov (1981), (5), 13-14
CODEN: PSGADK; ISSN: 0131-5498
DOCUMENT TYPE: Journal
LANGUAGE: Russian
ED Entered STN: 12 May 1984
IT **83-88-5P**, preparation
RL: IMF (Industrial manufacture); **PREP (Preparation)**
(ventilation waste gases from manufacture of, mercury removal from, method and apparatus for)
RN 83-88-5 CAPLUS
CN Riboflavin (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



L109 ANSWER 4 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN

AB The invention describes new pharmaceutical compns., their method of manufacture and use of these compns. to be administered as combination therapy for the treatment of cardiovascular and related disorders and cardiovascular disorders associated with hyperhomocysteinemia, in particular a combination of vitamins and folic acid with cholesterol lowering drugs or lipid regulators and antihypertensive agents, e.g., β-adrenergic blockers, calcium channel blockers, angiotensin converting enzyme inhibitors.

ACCESSION NUMBER: 2006:818202 CAPLUS Full-text
DOCUMENT NUMBER: 145:235852
TITLE: Cardiovascular therapeutic combinations
INVENTOR(S): Iyer, Eswaran Krishnan; Jha, Rasendrakumar Jayantilal; Saoji, Dilip Gopalkrishna
PATENT ASSIGNEE(S): Wockhardt Limited, India
SOURCE: PCT Int. Appl., 68pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006085128	A1	20060817	WO 2005-IB346	20050209

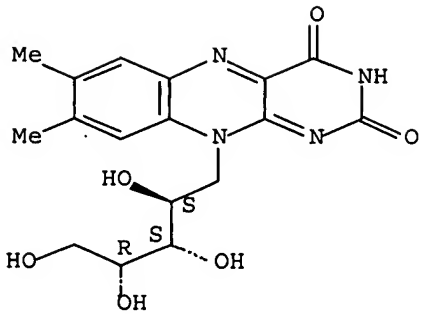
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: WO 2005-IB346 20050209
ED Entered STN: 17 Aug 2006

IT **83-88-5**, Riboflavin, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cardiovascular therapeutic combinations)

RN 83-88-5 CAPLUS
CN Riboflavin (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L109 ANSWER 5 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN

AB The invention provides a nutritional supplement which includes micronutrients to facilitate reduction of cholesterol, and/or reduction of homocysteine and/or reduction of low-d. lipoprotein-cholesterol (LDL-C) oxidation in humans. In one embodiment the supplement is a multivitamin and mineral supplement which includes at least one component known to reduce cholesterol. The invention further provides a method for tableting one fourth to one half of the daily effective dosage of a phytosterol-containing nutritional supplement in a practical sized tablet and a method for reducing blood cholesterol in humans.

ACCESSION NUMBER: 2005:1050505 CAPLUS Full-text
DOCUMENT NUMBER: 143:332601
TITLE: Multivitamin, mineral and anticholesteremic nutritional supplements
INVENTOR(S): Bubnis, William; Cotter, Richard; Herman, Paul W.; Moreines, Judith; Poxon, Scott W.; Sutton, Bruce W.; Vernon, Jeffrey V.; Walters, Denise L.; Williams, Michael G.; Wittenberg, Neil
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 18 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005214383	A1	20050929	US 2005-90486	20050328
AU 2005228421	A1	20051013	AU 2005-228421	20050328
CA 2560595	A1	20051013	CA 2005-2560595	20050328
WO 2005094333	A2	20051013	WO 2005-US10467	20050328
WO 2005094333	A8	20060105		
WO 2005094333	A3	20060216		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, SZ, BE, CY, FR, GR, IE, IT, MC, NL, SI, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1732605 A2 20061220 EP 2005-731047 20050328

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR

US 2006024352 A1 20060202 US 2005-236570 20050928

PRIORITY APPLN. INFO.: US 2004-557247P P 20040329

US 2005-90486 A2 20050328

WO 2005-US10467 W 20050328

ED Entered STN: 30 Sep 2005

IT **83-88-5**, Riboflavin, biological studies

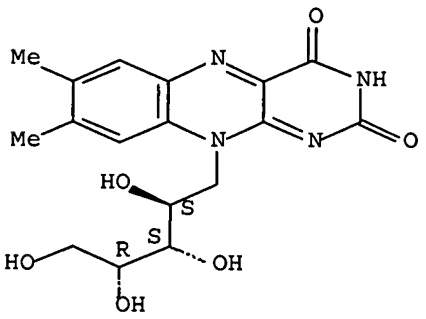
RL: FFD (Food or feed use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(multivitamin, mineral and anticholesteremic nutritional supplements)

RN 83-88-5 CAPLUS

CN Riboflavin (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



L109 ANSWER 6 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN

AB A process for the production of protein-vitamin concs. from sugar mill pre-defecation (pre-purification) or pre-saturation precipitate from sugar beet juice with the use of fermentation with yeasts Candida scottii KS-2 and Trichosporon cutaneum BD-2 has been described earlier. This study examined the protein, amino acid, vitamin, and mineral composition of the obtained protein-vitamin concs. The result indicated that the yeast-rich concs. had high levels of essential amino acids and some minerals. The concs. can be used as feed additives at 2-5% of the ration weight

ACCESSION NUMBER: 2005:844608 CAPLUS Full-text

DOCUMENT NUMBER: 144:169913

TITLE: Biological value of protein-vitamin concentrates obtained from pre-defecation **precipitate**

AUTHOR(S): Olyanskaya, S. P.; Kupchik, M. P.

CORPORATE SOURCE: Nats. Univ. Pishch. Tekhnol., Ukraine

SOURCE: Tsukor Ukraini (2005), (1-2), 44-46

CODEN: TUSKBU

PUBLISHER: Informatsiino-Analitichnii Tsentr "Tsukor Ukraini"

DOCUMENT TYPE: Journal

LANGUAGE: Russian

ED Entered STN: 22 Aug 2005

IT **83-88-5**, Vitamin b2, biological studies

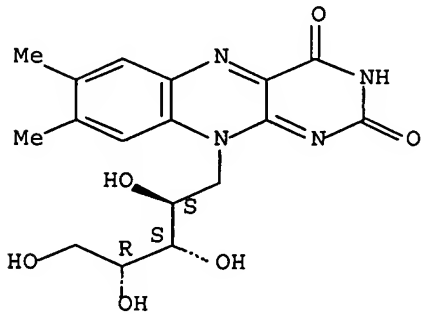
RL: FFD (Food or feed use); BIOL (Biological study); USES (Uses)

(nutritional value of protein-vitamin concs. obtained from sugar mill pre-defecation **precipitate** fermented with yeasts)

RN 83-88-5 CAPLUS

CN Riboflavin (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



L109 ANSWER 7 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN

AB A coated, uncooked oat product is provided that has no added fat and comprises uncooked oat flakes having a coating adherent to the oat flakes. A coated, oat flake agglomerate is also provided, wherein each agglomerate comprises at least two uncooked oat flakes and has a fat-free coating. A flavored, coated oat product in bulk and a flavored, coated, agglomerated oat product are provided, both of which have flavors uniformly distributed throughout the bulk. Corn grit products are also provided and include (1) individual pieces of corn grits having a fat-free coating and (2) clusters of corn grit pieces having a fat-free coating. A method of coating uncooked oat flakes with a desired fat-free coating to form the coated, uncooked oat product is also provided. The method involves feeding uncooked oat flakes into a circulating drum, coating the oat flakes by spraying the oat flakes with a stream of coating material, drying the coated oat flakes until the oat flakes have attained the desired moisture content, and cooling the coated oat flakes. Also provided is a method of forming uncooked oat flake agglomerates having a fat-free coating. This method involves essentially the same steps as the aforedescribed method. However, in the coating step of this method, the coating material sprayed onto the oat flakes comprises a binding material that allows the oat flakes to form agglomerates of at least two oat flakes. Also provided is a method of preparing the desired coating material.

ACCESSION NUMBER: 2001:526346 CAPLUS Full-text

DOCUMENT NUMBER: 135:91887

TITLE: Modified oat and corn grit products and method

INVENTOR(S): Hansa, James D.; Hibbs, Alice H.; Salisbury, Donald Kent

PATENT ASSIGNEE(S): The Quaker Oats Company, USA

SOURCE: U.S. Pat. Appl. Publ., 16 pp., Division of U. S. Ser. No. 487,036.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001008645	A1	20010719	US 2000-737906	20001215

US 6472004	B2	20021029		
US 2002044993	A1	20020418	US 2000-487036	20000119
US 6685976	B2	20040203		
US 2003031760	A1	20030213	US 2002-272804	20021017
US 2005031739	A1	20050210	US 2004-935676	20040907
US 7063866	B2	20060620		
AU 2007200100	A1	20070201	AU 2007-200100	20070110

PRIORITY APPLN. INFO.:

US 2000-487036	A3	20000119
US 2000-737906	A1	20001215
US 2002-272804	A1	20021017
AU 2003-262488	A3	20031124

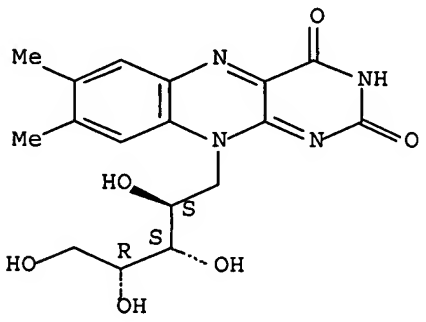
ED Entered STN: 20 Jul 2001

IT **83-88-5**, Riboflavin, biological studies
RL: FFD (Food or feed use); BIOL (Biological study); USES (Uses)
(modified uncooked oat flake and corn grit products and method of manufacture)

RN 83-88-5 CAPLUS

CN Riboflavin (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



L109 ANSWER 8 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN

AB Superparamagnetic particles consist of superparamagnetic 1-domain particles and aggregates of superparamagnetic 1-domain particles to whose surfaces are bound inorg. and optionally organic substances optionally having further binding sites for coupling to tissue-specific binding substances, diagnostic or pharmacol. active substances. The superparamagnetic particles consist of a mixture of small superparamagnetic 1-domain particles with a particle size from 3-50 nm and stable, degradable aggregates of small superparamagnetic 1-domain particles with a particle size from 10-1000 nm. They are made of Fe hydroxide, Fe oxide hydrate, Fe oxides, Fe mixed oxides or Fe to the surface of which are bound silicate group containing substances among the orthosilicic acids and their condensation products and phosphate-group containing substances among the ortho- or metaphosphoric acids and their condensation products. These substances may have further binding sites.

ACCESSION NUMBER:	2001:592182 CAPLUS Full-text
DOCUMENT NUMBER:	135:161519
TITLE:	Manufacture superparamagnetic particles and applications
INVENTOR(S):	Pilgrimm, Herbert
PATENT ASSIGNEE(S):	Germany
SOURCE:	U.S., 6 pp., Cont.-in-part of U.S. Ser. No. 776,131. CODEN: USXXAM
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6274121	B1	20010814	US 1999-300532	19990427
DE 4427821	A1	19960201	DE 1994-4427821	19940727
WO 9603653	A1	19960208	WO 1995-DE1028	19950727
W: JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 772776	A1	19970514	EP 1995-927635	19950727
EP 772776	B1	20000322		
R: AT, BE, CH, DE, FR, GB, IT, LI, NL, SE				
JP 10503281	T	19980324	JP 1996-505368	19950727
JP 3436760	B2	20030818		
AT 191086	T	20000415	AT 1995-927635	19950727
US 5928958	A	19990727	US 1997-776131	19970108

PRIORITY APPLN. INFO.:

DE 1994-4427821	A	19940727
WO 1995-DE1028	W	19950727
US 1997-776131	A2	19970108
DE 1993-4309333	A	19930317

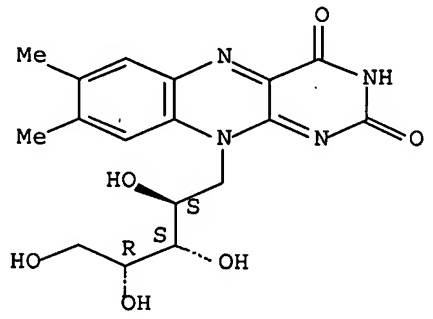
ED Entered STN: 15 Aug 2001

IT **83-88-5**, Riboflavin, processes
RL: PEP (Physical, engineering or chemical process); PROC (Process)
(residue of; process for manufacture and applications of superparamagnetic particles)

RN 83-88-5 CAPLUS

CN Riboflavin (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

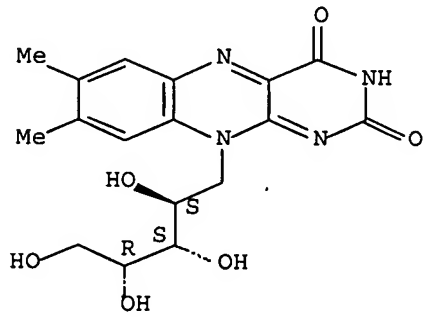
L109 ANSWER 9 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN

AB Two problems of an unacceptable nature were experienced during the formulation of effervescent multi-vitamin and mineral tablets. When tablets containing ascorbic acid, calcium carbonate and vitamins, combined with ordinary effervescent excipients and sodium benzoate as lubricant, were dissolved, fine needles formed during effervescence. These needless float on top of the solution, making the product unattractive. During effervescence of a second tablet containing magnesium oxide and calcium carbonate, combined with ascorbic acid, a flake-like sediment formed. IR spectrophotometry, differential scanning calorimetry and atomic absorption anal. showed that the needles were benzoic acid, while the flakes were citrates - mainly calcium citrate. These problems were overcome by substituting the benzoic acid with micronized polyethylene glycol 6000 and by not including citric acid during

the granulation stage but to add coarse citric acid crystals to the dry granules - composed of the rest of the tablet ingredients.

ACCESSION NUMBER: 1995:745960 CAPLUS Full-text
DOCUMENT NUMBER: 123:152796
TITLE: Identification and prevention of insoluble reaction products forming after dissolution of effervescent multi-vitamin tablets
AUTHOR(S): Lotter, A. P.; de Villiers, M. M.; Handford, J. S.; Liebenberg, W.
CORPORATE SOURCE: Inst. Industrial Pharmacy, Potchefstroom Univ., Potchefstroom, 2520, S. Afr.
SOURCE: Drug Development and Industrial Pharmacy (1995), 21(17), 1989-98
CODEN: DDIPD8; ISSN: 0363-9045
PUBLISHER: Dekker
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 18 Aug 1995
IT **83-88-5**, Riboflavin, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(interactions in effervescent multi-vitamin and **mineral** tablets)
RN 83-88-5 CAPLUS
CN Riboflavin (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



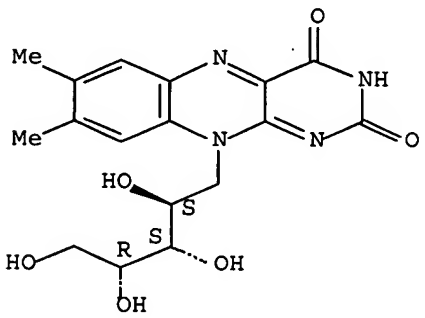
L109 ANSWER 10 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
AB The title apparatus, for the contacting of fluids with dispersed solids or solid-liquid dispersions, particularly for drying and granulating and coating purposes, consisting of a housing containing a rotatable base, a gas-supply slit between the inside wall of the housing and the base, a gas inlet to the system located below the base, and a mechanism for the addition of the materials to be treated and for the removal of the finished product, contains between the vertical centerline of the apparatus and the gas-supply slit between the base and the wall, ≥1 circular intermediate gas-supply slits and a concentrically located and preferably conical body that can be raised or lowered for material discharge. Coated sugar beet seeds 0.42 kg containing 33.6% water were dried in an apparatus of this type (diameter 0.184 m) with a total air flow of 45 Nm3/h. The base rotated at 180 rpm. To preserve the germinating properties of the seeds, the air temperature was kept low (at 45°). After 0, 3, 5, 10, 15, and 20 min, the temperature of the material and moisture content were 24.0, and 33.5, 18.5 and 27.3, 20.5 and 24.0, 28.0 and 14.7, 35.0 and 10.0, and 39.5° and 4.9 weight%, resp. The treatment was rapid and did not damage the product.

ACCESSION NUMBER: 1987:639220 CAPLUS Full-text
DOCUMENT NUMBER: 107:239220
TITLE: Apparatus and method for the contacting of materials in rotating, fluidized system
INVENTOR(S): Hajdu, Rudolf; Ormos, Zoltan; Horvath, Emese; Pataki, Karoly
PATENT ASSIGNEE(S): Magyar Tudomanyos Akademia, Muszaki Kemiai Kutato Intezet, Hung.
SOURCE: Ger. Offen., 16 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 3705343	A1	19870924	DE 1987-3705343	19870219
DE 3705343	C2	19950427		
HU 45701	A2	19880829	HU 1986-708	19860220
HU 196717	B	19890130		
FR 2598332	A1	19871113	FR 1987-2218	19870220
FR 2598332	B1	19910215		

PRIORITY APPLN. INFO.: HU 1986-708 A 19860220
ED Entered STN: 25 Dec 1987
IT **83-88-5**, Vitamin B2, uses and miscellaneous
RL: USES (Uses)
(in coating of vitamin C)
RN 83-88-5 CAPLUS
CN Riboflavin (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



L109 ANSWER 11 OF 39 CAPLUS COPYRIGHT 2007 ACS on STN
AB A charge of granules is coated on a horizontal rotor within a fixed shell by alternately feeding a powder and spraying a binder fluid, then drying under fully automatic control using elec.-conductivity and temperature sensor-transmitters to continuously monitor coating quality and actuate the feeders for the powder, the fluid, and the hot air supply. The rotor runs at 100-300 rpm and has smoothly curved surfaces such that the circumference is a little higher than most of the area and such that the surface curves upward to form a central elevated hub. Air is blown upward through a very narrow gap between the rotor and the wall to keep it clear, and an exhauster draws air and dust from the top to avoid pressure buildup. Hot air is fed for drying. The granules swirl and fall back repeatedly to the rotor. A plow can be added to

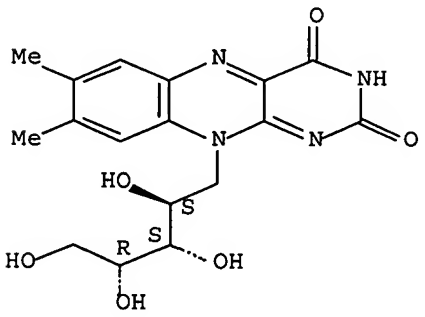
help move the particles. Also, rails mounted on the fixed wall at 5-70° above horizontal impart upward rotary motion. A fluoropolymer film on the rotor and fixed wall surfaces aids mixing. In examples, ascorbic acid, vitamins B2/B6 mixture, Ca pantothenate, or thiamine tetrahydrofurfuryl disulfide is coated onto a 1:1 sugar/corn starch mixture The product is uniform in quality and particle size, has a good spherical shape, does not clump together, and coating is rapid.

ACCESSION NUMBER: 1973:5848 CAPLUS Full-text
DOCUMENT NUMBER: 78:5848
TITLE: Coating of granular material
INVENTOR(S): Funakoshi, Yoshiro; Matsumura, Yoshihiko; Yamamoto, Masaki; Komeda, Hiromu
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd.
SOURCE: Ger. Offen., 29 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2165430	A	19720706	DE 1971-2165430	19711229
DE 2165430	B2	19740110		
DE 2165430	C3	19740801		
JP 54000992	B	19790118	JP 1970-128947	19701229
IT 943380	B	19730402	IT 1971-71274	19711229
CH 538816	A	19730831	CH 1971-19149	19711229
GB 1355828	A	19740605	GB 1971-60426	19711229
US 4034126	A	19770705	US 1975-621621	19751010
PRIORITY APPLN. INFO.:			JP 1970-128947 A	19701229
			US 1971-213608 A2	19711229
			US 1973-419964 A2	19731129

ED Entered STN: 12 May 1984
IT **83-88-5**, uses and miscellaneous
RL: USES (Uses)
(coating with, on starch-sugar granules)
RN 83-88-5 CAPLUS
CN Riboflavin (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



L109 ANSWER 12 OF 39 MEDLINE on STN
ACCESSION NUMBER: 73127390 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 4143949
TITLE: Red cell metabolism. A. Defects not causing hemolytic disease. B. Environmental modification.
AUTHOR: Beutler E
SOURCE: Biochimie, (1972) Vol. 54, No. 5, pp. 759-64.
Journal code: 1264604. ISSN: 0300-9084.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197304
ENTRY DATE: Entered STN: 10 Mar 1990
Last Updated on STN: 3 Mar 2000
Entered Medline: 26 Apr 1973
CONTROLLED TERM: Catalase: BL, blood
Cholinesterases: BL, blood
Enzyme Tests
*Erythrocytes: EN, enzymology
Flavin-Adenine Dinucleotide: TU, therapeutic use
Galactosemias
Glucosephosphate Dehydrogenase Deficiency
Glutathione Reductase: BL, blood
Humans
L-Lactate Dehydrogenase: BL, blood
Lesch-Nyhan Syndrome
*Metabolism, Inborn Errors
Metabolism, Inborn Errors: DT, drug therapy
NAD: TU, therapeutic use
NADP: TU, therapeutic use
Nicotinic Acids: TU, therapeutic use
Pyridoxine: TU, therapeutic use
Riboflavin: TU, therapeutic use
CAS REGISTRY NO.: 146-14-5 (Flavin-Adenine Dinucleotide); 53-59-8 (NADP); 53-84-9 (NAD); 65-23-6 (Pyridoxine); 83-88-5 (Riboflavin)
CHEMICAL NAME: 0 (Nicotinic Acids); EC 1.1.1.27 (L-Lactate Dehydrogenase); EC 1.11.1.6 (Catalase); EC 1.8.1.7 (Glutathione Reductase); EC 3.1.1.8 (Cholinesterases)

L109 ANSWER 13 OF 39 PASCAL COPYRIGHT 2007 INIST-CNRS. ALL RIGHTS RESERVED. on STN DUPLICATE 1
ACCESSION NUMBER: 2005-0304645 PASCAL Full-text
COPYRIGHT NOTICE: Copyright .COPYRGT. 2005 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Effects of a new pathogen-reduction technology (Mirasol PRT) on functional aspects of platelet concentrates
AUTHOR: PEREZ-PUJOL S.; TONDA R.; LOZANO M.; FUSTE B.; LOPEZ-VILCHEZ I.; GALAN A. M.; LI J.; GOODRICH R.; ESCOLAR G.
CORPORATE SOURCE: Hemotherapy-Hemostasis Service, CDB, Hospital Clinic, IDIBAPS, University of Barcelona, Spain; Navigant Biotechnologies, Inc, Lakewood, Colorado, United States
SOURCE: Transfusion : (Philadelphia, PA), (2005), 45(6), 911-919, 40 refs.
ISSN: 0041-1132 CODEN: TRANAT
DOCUMENT TYPE: Journal

BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-10224, 354000138495430130
ABSTRACT: BACKGROUND: Several strategies are being developed to reduce the risk of pathogen transmission associated with platelet (PLT) transfusion. STUDY DESIGN AND METHODS: The impact of a new technology for pathogen reduction based on **riboflavin** plus illumination (Mirasol PRT, Navigant Biotechnologies, Inc.) at 6.2 and 12.3 J per mL on functional and biochemical characteristics of PLTs was evaluated. PLT concentrates (PCs) obtained by apheresis were treated with Mirasol PRT and stored at 22.degree.C. **Modifications** in major PLT glycoproteins (GPIbα, GPIV, and GPIIb-IIIa), adhesive ligands (von Willebrand factor [VWF], fibrinogen [Fg], and fibronectin), activation antigens (P-selectin and LIMP), and apoptotic markers (annexin V binding and factor [F]Va) were analyzed by flow cytometry. Adhesive and cohesive PLT functions were evaluated with well-established perfusion models. Studies were performed on the **preparation** day (Day 0) and during PCs storage (Days 3 and 5). RESULTS: Levels of glycoproteins remained stable during storage in PCs treated with 6.2 J per mL pathogen reduction technology (PRT) and similar to those observed in nontreated PCs. When 12.3 J per mL PRT was applied, however, levels of GPIbα moderately decreased on Days 3 and 5. VWF, Fg, and FVa were not modified in their expression levels, either by treatment or by storage period. Fibronectin appeared more elevated in all PRT samples. A progressive increase in P-selectin and LIMP expression and in annexin V binding was observed during storage of PRT-treated PCs. Functional studies indicated that 6.2 J per mL Mirasol PRT-treated PLTs preserved adhesive and cohesive functions to levels compatible with those observed in the respective control PCs. CONCLUSION: PLT function was well preserved in PCs treated with 6.2 J per mL Mirasol PRT and stored for 5 days. CLASSIFICATION CODE: 002B27D01; Life sciences; Medical sciences; Transfusion
002A04I03; Life sciences; Biological sciences; Cell biology, Hematology
002B02G; Life sciences; Medical sciences; Pharmacology; Hematology
CONTROLLED TERM: Transfusion; Platelet; Concentrate

L109 ANSWER 14 OF 39 FROSTI COPYRIGHT 2007 LFRA on STN
ACCESSION NUMBER: 539757 FROSTI Full-text
TITLE: Process for **preparing** spray **granules** containing **riboflavin.**
INVENTOR: Nowotny M.; Tritsch J.-C.
PATENT ASSIGNEE: F. Hoffmann-la Roche AG
SOURCE: European Patent Application
PATENT INFORMATION: EP 1048668 A2
APPLICATION INFORMATION: 20000419
PRIORITY INFORMATION: European Patent Office 19990430
DOCUMENT TYPE: Patent
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT: A novel process is described for **manufacturing** flowable, dust-free **riboflavin granules. Riboflavin** crystals of crystal **modification B/C** are used for **preparing** an aqueous suspension that is subjected to spray drying. **Fluidized beds**, single fluid nozzles, or disk-type drying equipment may be used. The crystal **modifications B** and **C** are more soluble than the A form of **riboflavin**, and have adequate storage stability without reverting to the needle-shaped A form. The **granules** may be used for production of **riboflavin** in tablet form.
SUBJECT HEADING: ADDITIVES
CONTROLLED TERM: CRYSTALS; DRYING; EUROPEAN PATENT; **GRANULES**;

PATENT; PRODUCTION; **RIBOFLAVIN**; VITAMINS
DATA ENTRY DATE: 12 Dec 2000

L109 ANSWER 15 OF 39 CABA COPYRIGHT 2007 CABI on STN
ACCESSION NUMBER: 75:67350 CABA Full-text
DOCUMENT NUMBER: 19741418950
TITLE: Effect of dietary vitamin E level on fat storage, adipose tissue cellularity and energy expenditure in rats and mice fed a high-fat diet
AUTHOR: Lemonnier, D.; Gasquet, P. de; Griglio, S.; Naon, R.; Reynouard, F.; Tremolieres, J.
CORPORATE SOURCE: Inst. Scientifique et Technique de l'Alimentation CNAM, 292 rue Saint Martin, Paris 3eme, France.
SOURCE: Nutrition and Metabolism, (1974) Vol. 16, No. 1, pp. 15-29.
DOCUMENT TYPE: Journal
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Nov 1994
Last Updated on STN: 1 Nov 1994

ABSTRACT:
After a 24-h fast 4-week-old female mice were randomly assigned to 6 groups and were fed to appetite on a control low-fat diet, a high-fat diet or on a high-fat diet containing 1/5, 1/10, 1/20 or 1/40 of the basal amounts of thiamin, riboflavin, pyridoxine, calcium pantothenate and niacin, until over 7 months old. Average daily food intake was measured monthly. After death organs were weighed and femur length was measured. The size and number of adipocytes in parametrial adipose tissue and plasma cholesterol values were measured. The heart and aorta were examined histologically. Mice fed on the diet containing 1/40 of the basal amounts of B vitamins died before the end of the experiment. Those on the diet with 1/20 of the basal amounts of B vitamins were similar to controls, whereas all mice maintained on high-fat diets with more B vitamins showed increases in body, liver, kidney and heart weights and in the size and number of adipocytes in parametrial adipose tissue. Plasma cholesterol values were unchanged and no histological change was observed. Food intake was low on the diet with 1/40 basal vitamins but was similar on all other diets.Male Wistar rats were fed on a control low-fat diet (C2), a high-fat diet (L2) or on C2/50 and L2/50 obtained by reducing the amount of thiamin, riboflavin, pyridoxine, niacin and calcium pantothenate in C2 and L2 to 1/50 of the basal amounts. Rats were killed 1, 7 and 12 months later and organ weights, serum cholesterol and cellularity of perirenal adipose tissue were measured. Rats on diet L2 showed significant obesity after 1 month and that was later accompanied by hyperplasia of perirenal adipose tissue. Rats on L2/50 diet were obese compared with those on C2/50 diet and adipocyte number increased in the perirenal pads of old L2/50 animals, but less than in L2 animals. Serum cholesterol was not affected by the B vitamin content of the diets.Eight rats were given diet L2 and were pair-fed with 8 rats of same bodyweight receiving L2/50 diet to appetite. After 36 days bodyweights did not differ significantly. Rats on L2 diet showed a significant increase in fat deposits and a decrease in liver, kidney and heart weights compared with rats on L2/50 diet.Oxygen consumption and carbon dioxide output of 7-month-old rats fed on diets C2, L2, C2/50 and L2/50 were measured. No significant difference was observed.

CLASSIFICATION: VV120 Physiology of Human Nutrition; LL510 Animal Nutrition (Physiology)
SEQUENCE CODE: ZA; ZB; 0N; 0U; HE; CA; BE; NU; 1N
BROADER TERM: Muridae; rodents; mammals; vertebrates; Chordata; animals
CONTROLLED TERM: organs; kidneys; liver; heart; weight; body measurements; adipose tissue; ADIPOCYTES; lipids; vitamin B complex; thiamin; riboflavin; nicotinic

acid; pyridoxine; intake
SUPPLEMENTARY TERM: fat excess; vitamin B complex intake; count and size; excess; metabolic effects; **modification** by vitamin **B** complex intake; panthothenic acid; modification of metabolic effects of lipid excess
CAS REGISTRY NUMBER: 59-43-8; 83-88-5; 59-67-6; 65-23-6
ORGANISM NAME: RATS

L109 ANSWER 16 OF 39 CABA COPYRIGHT 2007 CABI on STN
ACCESSION NUMBER: 74:61449 CABA Full-text
DOCUMENT NUMBER: 19731415439
TITLE: Effect of single doses of riboflavin, vitamin B-6 and niacin on gastric secretion in duodenal ulcer
Vliyanie odnokratnogo vvedeniya vitaminov B2, B6 i PP na sekretornuyu funktsiyu zheludka pri yazvennoi bolezni dvenadtsatiperstnoi kishki
AUTHOR: Palei, L. F.
SOURCE: Klinicheskaya Meditsina, (1973) Vol. 51, No. 10, pp. 68-69.
ISSN: 0023-2149
DOCUMENT TYPE: Journal
LANGUAGE: Russian
ENTRY DATE: Entered STN: 1 Nov 1994
Last Updated on STN: 1 Nov 1994

ABSTRACT:
Injection by muscle of 40 mg riboflavin, 125 mg niacin or 150 mg vitamin B-6 had no significant effect on the amount of gastric fluid or on the pepsin-forming function of the stomach in groups of 10 or 11 patients with duodenal ulcer. Riboflavin and vitamin B-6 reduced total secretion of HCl and its concentration in gastric fluid but niacin had no such effect.

CLASSIFICATION: VV130 Nutrition Related Disorders and Therapeutic Nutrition
SEQUENCE CODE: ZB; 0U; HE; CA; NU; 1N
BROADER TERM: Homo; Hominidae; Primates; mammals; vertebrates; Chordata; animals
CONTROLLED TERM: stomach; secretion; acids; pyridoxine; GASTRIC JUICES; riboflavin; nicotinic acid; ulcers; vitamin B complex; duodenal ulcers
SUPPLEMENTARY TERM: **modification** by vitamin **B** complex; pepsin formation; duodenal ulcer patient; duodenal; acid stomach secretion
CAS REGISTRY NUMBER: 65-23-6; 83-88-5; 59-67-6
ORGANISM NAME: man

L109 ANSWER 17 OF 39 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN DUPLICATE 2
ACCESSION NUMBER: 2004:257874 BIOSIS Full-text
DOCUMENT NUMBER: PREV200400257993
TITLE: Process for **preparing** spray **granules** containing **riboflavin.**
AUTHOR(S): Nowotny, Markus [Inventor, Reprint Author]; Tritsch, Jean-Claude [Inventor]
CORPORATE SOURCE: Rheinfelden, Switzerland
ASSIGNEE: Roche Vitamins Inc.
PATENT INFORMATION: US 6723346 20040420
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Apr 20 2004) Vol. 1281, No. 3. http://www.uspto.gov/web/menu/patdata.html. e-file.

ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 12 May 2004
Last Updated on STN: 12 May 2004
ABSTRACT:The invention is concerned with a novel process for the ***manufacture*** of flowable, non-dusty, binder-free **riboflavin** ***granulates*** by subjecting an aqueous suspension of **riboflavin** crystals of crystal **modification B/C** to a ***fluidized*** **bed** spray drying process, a single fluid nozzle spray drying process or a disk-type spray drying process.
NAT. PATENT. CLASSIF.:424489000
CONCEPT CODE: Pathology - Therapy 12512
Pharmacology - General 22002
INDEX TERMS: Major Concepts
Methods and Techniques; Pharmaceuticals (Pharmacology)
INDEX TERMS: Methods & Equipment
riboflavin spray **granules**
preparation method: clinical techniques

L109 ANSWER 18 OF 39 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:537454 BIOSIS Full-text
DOCUMENT NUMBER: PREV200510332891
TITLE: The importance of (early) folate status to primary and secondary coronary artery disease prevention.
AUTHOR(S): Muskiet, Frits A. J. [Reprint Author]
CORPORATE SOURCE: Univ Groningen, Med Ctr, Dept Pathol and Lab Med, POB 30 001, NL-9700 RB Groningen, Netherlands
f.a.j.muskiet@lc.umcg.nl
SOURCE: Reproductive Toxicology, (SEP-OCT 2005) Vol. 20, No. 3, pp. 403-410.
CODEN: REPTED. ISSN: 0890-6238.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Dec 2005
Last Updated on STN: 1 Dec 2005
ABSTRACT:Folate, methionine, betaine, choline, zinc and Vitamins B-12, B-6 and B-2 are involved in one-carbon metabolism, which includes S-adenosylmethionine (SAM) substrated methylation. Inadequate enzyme activities and imbalances of substrates and cofactors in one-carbon metabolism, together referred to as the 'methyldietary' constituents, may cause homocysteine and S-adenosylhomocysteine accumulation. Hyperhomocysteinemia is associated with many disorders including coronary artery disease (CAD). CAD at adult age is also associated with low birth weight-induced 'programming', which prepares for unfavorable postpartum conditions and carries the potential of transgenerational transmission. CAD risks of hyperhomocysteinemia and 'programming' might find a common biochemical basis in epigenetics, which, among others, operates via SAM-substrated methylation of DNA and histones. Folic acid-responsive global and locus-specific hypomethylation were found in hyperhomocysteinemia and CAD. Currently, there is no hard evidence that folic acid supplementation of CAD patients is beneficial or that improved folate status in pregnancy prevents CAD in the offspring at adult age. The folate RDA as derived from CAD primary prevention might require embracement of the assumption that 'what nutritional measures are best for CAD patients are most probably best for the general population'. We have no knowledge on the optimal 'methyldiet' balance on which our genome has become adapted during millions of years of evolution and on which our genome consequently functions best. More insight may derive from the study of methyldietary constituents and soft endpoints such as plasma

homocysteine and gene methylation, in healthy, pregnant and non-pregnant, subjects and CAD patients and in populations with high and low CAD risks and those consuming diets more closely related to our ancient diet. Folic acid supplementation is obviously unnecessary at sufficient intake of naturally occurring folates, implying that continuing efforts should aim at meeting the recommendations by making the right choice of food products, that are either or not folate-enriched by genetic **modification.** (c) 2005 Elsevier Inc. All rights reserved.

CONCEPT CODE: Biochemistry studies - General 10060
Biochemistry studies - Vitamins 10063
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Minerals 10069
Pathology - General 12502
Nutrition - General studies, nutritional status and methods 13202
Cardiovascular system - Heart pathology 14506
Cardiovascular system - Blood vessel pathology 14508

INDEX TERMS: Major Concepts
Cardiovascular Medicine (Human Medicine, Medical Sciences); Nutrition; Biochemistry and Molecular Biophysics

INDEX TERMS: Diseases
coronary artery disease: heart disease, vascular disease, pathology, prevention and control
Coronary Disease (MeSH)

INDEX TERMS: Chemicals & Biochemicals
zinc; homocysteine; methionine; folate; choline; betaine; vitamin B-6; vitamin B-12; vitamin B-2; S-adenosylhomocysteine

INDEX TERMS: Miscellaneous Descriptors
one-carbon metabolism

ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common)
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

REGISTRY NUMBER: 7440-66-6 (zinc)
6027-13-0 (homocysteine)
63-68-3 (methionine)
59-30-3 (folate)
62-49-7 (choline)
107-43-7 (betaine)
8059-24-3 (vitamin B-6)
68-19-9 (vitamin B-12)
83-88-5 (vitamin B-2)
979-92-0 (S-adenosylhomocysteine)

L109 ANSWER 19 OF 39 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 2000:493309 BIOSIS Full-text
DOCUMENT NUMBER: PREV200000493430
TITLE: Modification of vitamins B1 and B2 by culinary processes: Traditional systems and microwaves.
AUTHOR(S): Orzaez Villanueva, M. T. [Reprint author]; Diaz Marquina, A.; Franco Vargas, E.; Blazquez Abellan, G.

CORPORATE SOURCE: C/Isla de Arosa no. 2, 12B, 28035, Madrid, Spain
SOURCE: Food Chemistry, (December, 2000) Vol. 71, No. 4, pp. 417-421. print.
CODEN: FOCHDJ. ISSN: 0308-8146.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Nov 2000
Last Updated on STN: 10 Jan 2002

ABSTRACT:Loss of thiamin and riboflavin is studied in Swiss chard and green beans. The processes of boiling and boiling and frying lightly in two systems, traditional and microwaves, both cause loss of these two vitamins, but vitamin B1 shows a higher loss in traditional boiling. Leaching of both vitamins into the boiling water occurs and, in general, Swiss chards show higher leaching losses, mainly in the traditional systems.

CONCEPT CODE: Food technology - General and methods 13502
Biochemistry studies - Vitamins 10063
Food technology - Fruits, nuts and vegetables 13504
INDEX TERMS: Major Concepts
Foods
INDEX TERMS: Chemicals & Biochemicals
riboflavin; thiamin; vitamin B-1: **modification**; vitamin B-2: **modification**
INDEX TERMS: Methods & Equipment
boiling: food processing method; frying: food processing method; microwave: food processing equipment
INDEX TERMS: Miscellaneous Descriptors
culinary processing; green beans: vegetable; swiss chard: vegetable
REGISTRY NUMBER: **83-88-5** (riboflavin)
59-43-8 (thiamin)
59-43-8 (vitamin B-1)
83-88-5 (vitamin B-2)

L109 ANSWER 20 OF 39 TOXCENTER COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:624746 TOXCENTER Full-text
DOCUMENT NUMBER: RISKLINE-2001090010
TITLE: Safety evaluation of certain food additives. Riboflavin derived by formulation with genetically modified bacillus subtilis
AUTHOR(S): FAO and W H O working groups
SOURCE: WHO Food Additives Series, (1999) 42 79-91.
FILE SEGMENT: RISKLINE
LANGUAGE: English
ENTRY DATE: Entered STN: 31 May 2005
Last Updated on STN: 3 Aug 2005

ABSTRACT:
The Committee concluded that the recombinant DNA techniques used to derive the production strain of B. subtilis were well characterized, providing assurance that no DNA is present in the end-product. On the basis of molecular biological data and chemical analytical research, it can be concluded that fermentation-derived riboflavin from genetically **modified B**
. subtilis is substantially equivalent to synthetic riboflavin. For 98% pure fermentation-derived riboflavin for use in food, the NOEL in the 90-day study of toxicity in rats was 200 mg/kg bw per day, the highest dose tested. Fermentation-derived riboflavin was evaluated on the basis of its substantial equivalence to synthetic riboflavin. Therefore, the Committee included riboflavin derived from a production strain of genetically **modified** ***B.*** subtilis in the previously established group ADI of 0-0.5 mg/kg bw for synthetic riboflavin and riboflavin-5'-phosphate.

SUPPLEMENTARY TERMS: Miscellaneous Descriptors
ANIMAL; acute toxicity; subchronic toxicity; genetic toxicity; blood
REGISTRY NUMBER: 130-40-5; 83-88-5

L109 ANSWER 21 OF 39 DPCI COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-681202 [67] DPCI
DOC. NO. CPI: C2000-207345
TITLE: Binder-free **riboflavin granulate** production, by spray-drying aqueous suspension of **riboflavin** crystals in **modification** B/C, giving soluble, compressible product useful for producing solutions or tablets.
DERWENT CLASS: B02 P33
INVENTOR(S): NOWOTNY, M; TRITSCH, J; NAOTENI, M; TERRIZ, J
PATENT ASSIGNEE(S): (HOFF) HOFFMANN LA ROCHE LTD F; (HOFF) HOFFMANN LA ROCHE & CO AG F; (STAM) DSM IP PROPERTY BV; (HOFF) HOFFMANN LA ROCHE & CO KG F; (STAM) DSM IP ASSETS BV; (HOFF) ROCHE VITAMINS INC
COUNTRY COUNT: 34
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
EP 1048668	A2	20001102	(200067)*	EN	8	C07D475-14
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI						
AU 2000030189	A	20001102	(200067)			C07D475-14
BR 2000002390	A	20001031	(200067)			C07D475-14
NO 2000002283	A	20001031	(200067)			A61K031-525
CA 2306502	A1	20001030	(200103)	EN		A61K031-525
JP 2000327562	A	20001128	(200110)		7	A61K009-16
CN 1275375	A	20001206	(200118)			A61K009-16
KR 2001029668	A	20010406	(200162)			A61J003-06
EP 1048668	B1	20030129	(200309)	EN		C07D475-14
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE						
DE 60001286	E	20030306	(200325)			C07D475-14
ES 2189711	T3	20030716	(200356)			C07D475-14
MX 2000004185	A1	20020501	(200368)			A61K009-16
US 6723346	B1	20040420	(200427)			A61K009-14
AU 770320	B2	20040219	(200453)			C07D475-14
MX 220559	B	20040525	(200501)			A61K009-16
NO 318219	B1	20050221	(200515)			A61K031-525
CN 1198595	C	20050427	(200641)			A61K009-16

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 1048668	A2	EP 2000-108560	20000419
AU 2000030189	A	AU 2000-30189	20000428
BR 2000002390	A	BR 2000-2390	20000428
NO 2000002283	A	NO 2000-2283	20000428
CA 2306502	A1	CA 2000-2306502	20000420
JP 2000327562	A	JP 2000-126926	20000427
CN 1275375	A	CN 2000-118052	20000428
KR 2001029668	A	KR 2000-22706	20000428
EP 1048668	B1	EP 2000-108560	20000419
DE 60001286	E	DE 2000-00001286	20000419
		EP 2000-108560	20000419

ES 2189711	T3	EP 2000-108560	20000419
MX 2000004185	A1	MX 2000-4185	20000428
US 6723346	B1	US 2000-550971	20000417
AU 770320	B2	AU 2000-30189	20000428
MX 220559	B	MX 2000-4185	20000428
NO 318219	B1	NO 2000-2283	20000428
CN 1198595	C	CN 2000-118052	20000428

FILING DETAILS:

PATENT NO	KIND	PATENT NO
DE 60001286	E Based on	EP 1048668
ES 2189711	T3Based on	EP 1048668
AU 770320	B2Previous Publ.	AU 2000030189
NO 318219	B1Previous Publ.	NO 2000002283

PRIORITY APPLN. INFO: EP 1999-108476 19990430
INT. PATENT CLASSIF.:
MAIN: A61J003-06; A61K009-14; A61K009-16; A61K031-525; C07D475-14
SECONDARY: A61J003-10; A61K009-20; A61K009-26; A61P003-02; B05D007-00
FILE SEGMENT: CPI GMPI

EXF EXAMINER'S FIELD OF SEARCH UPE: 20040613

NCL US 6723346 B1 20040420
000/424.464; 000/424.465; 000/424.470; 000/424.489; 000/427.213

IC EP 1048668 B1 20030129
C07D475--14

CTCS CITATION COUNTERS

PNC.DI	0	Cited Patents Count (by inventor)
PNC.DX	13	Cited Patents Count (by examiner)
IAC.DI	0	Cited Issuing Authority Count (by inventor)
IAC.DX	2	Cited Issuing Authority Count (by examiner)
PNC.GI	0	Citing Patents Count (by inventor)
PNC.GX	3	Citing Patents Count (by examiner)
IAC.GI	0	Citing Issuing Authority Count (by inventor)
IAC.GX	1	Citing Issuing Authority Count (by examiner)
CRC.I	0	Cited Literature References Count (by inventor)
CRC.X	1	Cited Literature References Count (by examiner)
OSC.D	9	Cited Patent WPI Accession Number Count
OSC.G	3	Citing Patent WPI Accession Number Count

CDP CITED PATENTS UPD: 20040613

Cited by Examiner

CITING PATENT	CAT	CITED PATENT	ACCNO

EP 1048668 A A EP 307767 A 1989-087185/12
PA: (HOFF) HOFFMANN-LA ROCHE AG
IN: HERENA, L E; RAMANARAYA, K
A EP 345717 A 1989-365498/50
PA: (BADI) BASF AG
IN: BUEHLER, W; EIPPER, G; GRIMMER, J; KIEFER, H; MARTIN, C; MEYER, J
YD EP 414115 A 1991-059372/09
PA: (BADI) BASF AG
IN: BUEHLER, V; PETERSEN, H
YD EP 457075 A 1991-333665/46
PA: (BADI) BASF AG; (GRIM-I) GRIMMER J
IN: GRIMMER, J; KIEFER, H; MARTIN, C
EP 995749 A 2000-294952/26
PA: (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) ROCHE VITAMINS INC
IN: WAGNER, G
A US 4994458 A 1991-072935/10
PA: (BADI) BASF CORP
IN: KILBRIDE, T K
A US 5000888 A 1991-101430/14
PA: (BADI) BASF CORP
IN: KILBRIDE, T K; LISA, R E
YD US 5300303 A 1991-333665/46
PA: (BADI) BASF AG; (GRIM-I) GRIMMER J
IN: GRIMMER, J; KIEFER, H; MARTIN, C

EP 1048668 B1 EP 307767 A 1989-087185/12
PA: (HOFF) HOFFMANN-LA ROCHE AG
IN: HERENA, L E; RAMANARAYA, K
EP 345717 A 1989-365498/50
PA: (BADI) BASF AG
IN: BUEHLER, W; EIPPER, G; GRIMMER, J; KIEFER, H; MARTIN, C; MEYER, J
EP 414115 A 1991-059372/09
PA: (BADI) BASF AG
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EP 457075 A 1991-333665/46
PA: (BADI) BASF AG; (GRIM-I) GRIMMER J
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EP 995749 A 2000-294952/26
PA: (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) ROCHE VITAMINS INC
IN: WAGNER, G
US 4994458 A 1991-072935/10
PA: (BADI) BASF CORP
IN: KILBRIDE, T K
US 5000888 A 1991-101430/14
PA: (BADI) BASF CORP
IN: KILBRIDE, T K; LISA, R E
US 5300303 A 1991-333665/46
PA: (BADI) BASF AG; (GRIM-I) GRIMMER J
IN: GRIMMER, J; KIEFER, H; MARTIN, C

US 6723346 B1 EP 414115 A 1991-059372/09
PA: (BADI) BASF AG
IN: BUEHLER, V; PETERSEN, H
EP 457075 A 1991-333665/46
PA: (BADI) BASF AG; (GRIM-I) GRIMMER J
IN: GRIMMER, J; KIEFER, H; MARTIN, C
EP 995749 A1 2000-294952/26
PA: (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) ROCHE

VITAMINS INC
IN: WAGNER, G
US 4977190 A 1989-365498/50
PA: (BADI) BASF AG
IN: BUEHLER, W; EIPPER, G; GRIMMER, J; KIEFER, H; MARTIN, C; MEYER, J
US 5137732 A 1991-059372/09
PA: (BADI) BASF AG
IN: BUEHLER, V; PETERSEN, H
US 5236920 A 1993-272139/34
PA: (BADI) BASF CORP
IN: KILBRIDE, T K; LISA, R E; TUMAN, W J
US 5300303 A 1991-333665/46
PA: (BADI) BASF AG; (GRIM-I) GRIMMER J
IN: GRIMMER, J; KIEFER, H; MARTIN, C
US 6093715 A 2000-514118/46
PA: (BADI) BASF CORP; (BADI) BASF AG
IN: DOUGLAS, N S; HARZ, H; SCHWEIKERT, L; SCHMIDT, D N

REN LITERATURE CITATIONS UPR: 20040613

Citations by Examiner

CITING PATENT	CAT	CITED LITERATURE
US 6723346	B1	Derwent English language abstract of EP 0 995 749 A1 (Document B3).

CGP CITING PATENTS UPG: 20050816

Cited by Examiner

CITED PATENT	CAT	CITING PATENT	ACCNO
EP 1048668	A2 AD	WO 2003092851 A	2003-903596/82
	PA:	(ACCE-N) ACCENTUS PLC	
	IN:	MCCAUSLAND, L J; REAY, D	
	YD	WO 2004089889 A2	2004-748715/72
	PA:	(BADI) BASF AG	
	IN:	FRANKE, D; HILL, F; KNEBEL, T; MARTIN, C	
	A	WO 2005014594 A1	2005-182056/12
	PA:	(STAM) DSM IP ASSETS BV	
	IN:	GLOOR, A	

L109 ANSWER 22 OF 39 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2006-063812 [07] WPIX
DOC. NO. CPI: C2006-023583 [07]
TITLE: Coated liquid-filled soft capsule, useful for administering e.g. vitamin products and nutritional supplements, comprises a liquid fill, a soft capsule shell and a coating applied on the exterior surface
DERWENT CLASS: A96; B07; D13; E24
INVENTOR: CHIPRICH T B

PATENT ASSIGNEE: (CHIP-I) CHIPRICH T B
COUNTRY COUNT: 1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 20050152969	A1	20050714	(200607)*	EN	10[0]	A61K009-48

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 20050152969	A1	US 2004-754458	20040108

PRIORITY APPLN. INFO: US 2004-754458 20040108
INT. PATENT CLASSIF.:
IPC RECLASSIF.: A61K0009-48 [I,A]; A61K0009-48 [I,C]
BASIC ABSTRACT:
US 20050152969 A1 UPAB: 20060130
NOVELTY - Coated liquid-filled soft capsule (I) comprises a liquid fill (a), a soft capsule shell (b) (formed from a material, which further comprises a colorant incorporated in it to provide a visual contrast between the capsule shell and any liquid fill that escapes from (b) and resides on an exterior surface of (b)) encapsulating (a) and a coating applied on the exterior surface.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method of making (I).
ACTIVITY - Immunostimulant; Anorectic; Anabolic.
MECHANISM OF ACTION - None given.
USE - The invention deals with coated liquid-filled soft capsule (claimed), specifically colored liquid filled soft capsules, which are useful for the administration of different types of active pharmaceuticals, vitamin products and nutritional supplements.
ADVANTAGE - (I) is an improved form of soft capsule and the preparative method is also an improved method, which is cost effective. The improvement in this invention is that by coloring (b) with a different color than the internal liquid filling, it is easier to detect and remove leakers. The coloring of the shell minimizes the exposure of the active ingredients to light. The soft capsules provide improved bioavailability, enhanced drug stability due to less exposure of the active ingredient to oxygen, excellent dose uniformity and product differentiation (e.g. through new shapes). The other advantages include patient compliance, consumer preference, speed of product development and short manufacturing time.
MANUAL CODE: CPI: A08-E01; A12-V01; B03-A; B03-C; B03-L; B04-A08C2; B04-A10; B04-B01C; B04-B03A; B04-B04M; B04-C02; B04-C03; B04-D01; B04-D02; B04-L01; B04-N02; B05-A01B; B05-A03A2; B05-A03A3; B05-A03A4; B05-A03B; B05-B02C; B05-C06; B06-D01; B06-D02; B06-D09; B06-D18; B07-A02B; B07-D08; B10-A01; B10-A09B; B10-E02; B11-C09; B12-M11C; B12-M18; B14-E11; B14-E12; B14-G01; B14-S08; D03-H01T2; E05-L02A; E06-D09; E10-C04H; E10-E02D3; E21-B05; E22-B05; E23-A02; E25-B03; E25-D; E25-E01; E25-E02; E25-E03; E31-C; E31-N04D; E31-P02D; E31-P04; E32-B; E34-C02; E34-D02; E34-D03A; E35-C; E35-K02; E35-P; E35-U02; E35-U03; E35-V
TECH
PHARMACEUTICALS - Preparation (claimed): Preparation of (I) comprises encapsulating (a) with (b), determining that (a) has not escaped the encapsulation of (b) such that the capsule is suitable for a coating

applied on the exterior surface and applying a coating to the capsule suitable for the coating on the exterior surface.
Preferred Components: The material comprises gelatin (which is natural gelatin, chemically or enzymatically modified gelatin) or a heat sealable polymer. The material further comprises an extender (which is natural and modified natural biopolymers or synthetic polymers). The natural biopolymer is starch or its derivatives, bacterial polysaccharides or gum. The modified natural biopolymer is **modified** cellulose. (**b**) comprises about 20% (preferably 60%) material. (a) comprises an active pharmaceutical agent, a vitamin, a mineral, an antioxidant, an enzyme, an immunostimulant, a weight loss product, an energy product or a nutritional supplement. (a) comprises a nutritional oil, which further comprises a stabilizer and the stabilizer is an antioxidant. The nutritional oil comprises omega-3 fatty acids, omega-6 fatty acids and/or essential fatty acids (preferably an essential fatty acid). The nutritional oil is fish oil and/or flaxseed oil. (a) further comprises a colorant, which is a pigment and/or a dye. The colorant is titanium dioxide (preferred), zinc oxide, iron oxides, iron hydroxides, calcium carbonate, calcium sulfate, curcumin, **riboflavin**, tartrazine, quinoline yellow, carmoisine, indigo carmine, chlorophylls, copper complexes of chlorophylls, lissamine green, caramel, charcoal, carotenoids, xanthophylls, anthocyanins, alumina, aluminum powder, annatto extract, bismuth oxychloride, bronze powder, canthaxanthin, chromium-cobalt-aluminum oxide, chromium hydroxide green, cochineal extract, carmine, copper powder, ferric ammonium citrate, ferric ammonium ferrocyanide, ferric ferrocyanide, guanine, logwood extract, mica, potassium sodium copper chlorophyllin, pyrogallol, ptrophyllite, talc, annatto extract, FD and C dyes, aluminum lake forms of FD and C dyes, D and C dyes or aluminum lake forms of D and C dyes. The gelatin capsule has a wet seal thickness of about 0.006 (preferably 0.025-0.035) inches. (I) further comprising an exterior finishing coat and the coating is an enteric coating. The coating comprises cellulose, vinyl, glycol, acrylic or carbohydrate polymers and further comprises a plasticizer, a processing aid and an edible fragrant substance. The coating substantially lacks a colorant.
Preferred Method: The step of determining that (a) has not escaped the encapsulation of (b) is determined visually.

L109 ANSWER 23 OF 39 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-191222 [18] WPIX
DOC. NO. CPI: C2004-075453 [18]
TITLE: Composition useful to modify cardiovascular health risk indicators e.g. cholesterol levels comprises single strength orange juice and soy protein
DERWENT CLASS: B05; D13
INVENTOR: GREEN N; MCARDLE R N; MCGILL C; MELLICAN R; PARSHALL K
PATENT ASSIGNEE: (GREE-I) GREEN N; (MCAR-I) MCARDLE R N; (MCGI-I) MCGILL C; (MELL-I) MELLICAN R; (PARS-I) PARSHALL K; (TROP-N) TROPICANA PROD INC
COUNTRY COUNT: 100

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2004011016	A1	20040205	(200418)*	EN	21[0]	A61K035-78
US 20040022877	A1	20040205	(200418)	EN		A61K035-78
AU 2003256920	A1	20040216	(200453)	EN		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004011016 A1		WO 2003-US23521	20030729
US 20040022877 A1		US 2002-209216	20020730
AU 2003256920 A1		AU 2003-256920	20030729

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003256920 A1	Based on	WO 2004011016 A

PRIORITY APPLN. INFO: US 2002-209216 20020730
INT. PATENT CLASSIF.:
IPC RECLASSIF.: A23L0002-02 [I,C]; A23L0002-06 [I,A]; A23L0002-52 [I,C]; A23L0002-66 [I,A]; A61P0009-00 [I,A]; A61P0009-00 [I,C]

BASIC ABSTRACT:

WO 2004011016 A1 UPAB: 20050528

NOVELTY - Treatment of individuals to modify cardiovascular health risk indicators involves administering a soy fortified orange juice composition (C). (C) comprises single strength orange juice and soy protein (at least 0.1, preferably at least 0.2 weight%). (C) **modifies** cholesterol levels to enhance the health of an individual.

ACTIVITY - Cardiovascular-Gen.; Antilipemic.

MECHANISM OF ACTION - None given.

USE - To modify cardiovascular health risk indicators e.g. cholesterol levels and blood pressure levels (claimed).

ADVANTAGE - (C) **modifies** cholesterol levels of the individual in at least one health-enhancing manner i.e. raises the high-density lipoprotein (HDL) cholesterol level or lowers the low-density lipoprotein (LDL) cholesterol level, particularly lowers the LDL to HDL cholesterol ratio by at least 0.1 (preferably 0.3, especially 0.5). (C) lowers the systolic blood pressure level of the individual by at least 2 mmHg. The essential nutrient in citrus juice is vitamin C that decreases the susceptibility of lipoproteins to oxidation; potassium linked to reduced risk of hypertension; and vitamin E that contributes to cardiovascular health enhancement. The soy fortified orange juice product showed that the soy fortification had only low color impact on the orange juice coloration, imparted only a very low bean or vegetable flavor to the juice, gave no grittiness, and added no thickness or viscosity to the orange juice. The combination of orange juice and soy protein has good soy availability, stability and high solubility within the orange juice to produce beneficial changes that enhances cardiovascular health. MANUAL CODE:
CPI: B03-B; **B03-C**; B03-D; B03-E; B03-F; B03-H; B04-B01B; B05-A01A; B05-A03A; B14-F01; B14-F02; B14-F06; D03-H01T2

TECH

ORGANIC CHEMISTRY - Preferred Composition: (C) additionally includes a nutrient selected from a folate, iron, potassium, B vitamins, vitamin E and vitamin C. (C) further includes ingredients with nutritional value which are in addition to those found in the juice or soy. The soy protein is present at a level of not more than 12.5 wt.%. The orange juice has a pH of 3.2 - 4.4.

Preferred Component: The soy protein is a soy protein hydrolysate having a short-chained peptide structure.

L109 ANSWER 24 OF 39 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2005-047199 [05] WPIX
DOC. NO. CPI: C2005-016046 [05]
TITLE: Composition, useful to treat cancer in mammal, comprises an aqueous alkali metal salt solution

DERWENT CLASS: B05
INVENTOR: GILES B C
PATENT ASSIGNEE: (GILE-I) GILES B C
COUNTRY COUNT: 1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 20040253323	A1	20041216	(200505)*	EN	12[0]	A61K031-59

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 20040253323	A1 Provisional	US 2003-477678P	20030611
US 20040253323	A1	US 2004-867115	20040614

PRIORITY APPLN. INFO: US 2004-867115 20040614
US 2003-477678P 20030611
INT. PATENT CLASSIF.:
IPC RECLASSIF.: A61K0031-352 [I,A]; A61K0031-352 [I,C]; A61K0031-4965 [I,A]; A61K0031-4965 [I,C]; A61K0031-59 [I,A]; A61K0031-59 [I,C]; A61K0033-04 [I,A]; A61K0033-04 [I,C]; A61K0033-06 [I,A]; A61K0033-06 [I,C]; A61K0033-24 [I,A]; A61K0033-24 [I,C]; A61K0038-23 [I,A]; A61K0038-23 [I,C]; A61K0045-00 [I,C]; A61K0045-06 [I,A]

BASIC ABSTRACT:

US 20040253323 A1 UPAB: 20050707

NOVELTY - Composition (I) comprises an aqueous alkali metal salt solution (A) for the treatment of cancer in mammal.

DETAILED DESCRIPTION - Composition (I) comprises an aqueous alkali metal salt solution (A) of formula MA(aq) for the treatment of cancer in mammal, where MA dissociates in water to form M+ and A-. M = an alkali metal (cesium and/or rubidium); and A = an anion (chloride, sulfate, carbonate, phosphate, lactate, citrate or acetate).

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - Protease tumor secretion inhibitor; Angiogenesis inhibitor.

USE - (I) is useful to treat cancer in mammal (claimed). No details of tests for treatment of cancer are given. MANUAL CODE: CPI: B02-B; **B03-C**; B03-E; B03-G; B04-J04A; B05-A01A; B05-A01B; B05-A03A; B05-B01D; B05-B02C; B07-A02; B07-D11; B10-A09B; B14-E11; B14-F02A; B14-G01; B14-H01; B14-H03

TECH

PHARMACEUTICALS - Preferred Composition: (I) further includes at least one substance such as
(a) vitamin D, selenium salts, calcitonin or calcium ionophores to stimulate calcium accumulation;
(b) monensin or sodium/potassium exchange inhibitors to reduce the elimination of sodium from cancer cells;
(c) pH-**modifying** nigericin, amiloride, 4,4'-diisothiocyanostilbene 2,2-disulfonic acid or bafilomycin to decrease acidity at the tumor site and systemic acidity;
(d) substance to depress glucose utilization by tumor cells or increase the activation of apoptosis;
(e) magnesium, zinc, **vitamin B2** or vitamin B12 to stimulate the immune system;
(f) substance that complements cesium and/or rubidium therapy by unrelated

means and may be useful in reducing cancer viability, well known compounds commonly used in chemotherapies that do not target ionic physiology; and (g) potassium, anti-oxidants or mineral supplements (trace minerals) to compensate for potassium loss due to any diuretic effect of the therapy. Preferred Components: Alkali metal salt is cesium citrate (400 mg) and/or rubidium citrate (100 mg) in an amount of 250- 2,500 mg or cesium chloride and/or rubidium chloride in an amount of 200 mg-10 grams of alkali salt/l of water. (A) is buffered and is isotonic to blood. (A) further includes 125-1000 mg of a potassium salt (potassium phosphate, potassium gluconate or potassium acetate), 1,250 mg calcium, 100-1,250 mg magnesium citrate, iodine, 50-150 mcg selenomethionine, 1-5 mcg vanadyl sulfate, 25-100 mg zinc gluconate, 1,000-2,000 international unit (IU) vitamin D, 1,000-2,500 international unit (IU) vitamin A, 500-2-500 mg buffered vitamin C (L-ascorbic acid), 50-250 mg malic acid, 12.5-25 mg COq; 2.5-25 mg dehydroepiandroststerone, 10-15 mg B3 methyl nicotinate 12.5-50 mg B6 and 10-25 mcg B12. Preferred Method: (A) is processed for formulation into dry tablet (capsule suitable for the long term treatment of cancer) or powdered form; and treatment of cancer further includes the step of monitoring pH and adjusting the therapy so that the systemic pH, the tumor pHe (pH of the micro environment of the tumor cells) and pHi (pH within the tumor cells) fall within a predetermined range. (I) is administered via body cavity or directly to cancerous neoplasms.

L109 ANSWER 25 OF 39 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-178633 [17] WPIX
DOC. NO. CPI: C2004-070694 [17]
TITLE: Antler extract mixture, useful for synthesis of stable compositions, comprises velvet antler powder, amino acids, carbohydrates, vitamins and minerals
DERWENT CLASS: A96; B05
INVENTOR: CHEN E S; HSU D H; SIRU C; XIAOLING X
PATENT ASSIGNEE: (CHEN-I) CHEN S; (USGO-C) US GOVERNMENT; (CHEN-I) CHEN E S
COUNTRY COUNT: 2

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 20030228372	A1	20031211	(200417)*	EN	10[0]	A61K035-32
CN 1466954	A	20040114	(200424)#	ZH		A61K035-32
US 7005144	B2	20060228	(200616)	EN		
CN 1195528	C	20050406	(200641)#	ZH		A61K035-32

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 20030228372	A1	US 2002-325746	20021223
CN 1466954	A	CN 2002-141031	20020711
CN 1195528	C	CN 2002-141031	20020711

PRIORITY APPLN. INFO: TW 2002-112440 20020607
TW 2002-112441 20020607
TW 2002-112442 20020607
CN 2002-141031 20020711
INT. PATENT CLASSIF.:
MAIN: A61K035-32
IPC ORIGINAL: A61K0035-32 [I,A]; A61K0035-32 [I,C]
IPC RECLASSIF.: A61K0031-185 [I,C]; A61K0031-198 [I,A]; A61K0031-70 [I,A]

; A61K0031-70 [I,C]; A61K0035-32 [I,A]; A61K0035-32 [I,C]
; A61K0009-16 [I,A]; A61K0009-16 [I,C]; A61P0001-00 [I,C]
; A61P0001-14 [I,A]

BASIC ABSTRACT:

US 20030228372 A1 UPAB: 20050528

NOVELTY - Antler extract mixture (I) comprises 70-90 wt% of velvet antler powder (A), 2-10 wt% of amino acid (B), 1-5 wt% of carbohydrate (C), 0.1-2 wt% of vitamin (D) and 0.1-3 wt% of minerals (E).

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for an antler composition (II) comprising (I) and a matrix (that comprises beta-cyclodextrin (J), a higher ester compound (K), a proteinase inhibitor (L) and an organic solvent (M)) in the weight ratio 1.5:1-2.7:1.

ACTIVITY - Immunostimulant.

MECHANISM OF ACTION - None given in the source material.

USE - Velvet antler extract provides polymeric materials that boost the immune system and are anti-aging and anti-disease agents.

ADVANTAGE - (I) provides velvet antler extract of high quality and quantity that can be used to make a composition (II) that retains the therapeutic properties of the extract and maintains its stability, while allowing non-oral administration that prevents degradation of the extract by stomach acids. (II) was subjected to comparative tests to determine its stability. The results revealed (II) to remain stable and homogenized with a high amount of antler even after 6 months. MANUAL CODE: CPI: A03-A00A; A12-V01; B03-L; B04-B04E; B04-C02; B04-C03C; B05-A01B; B05-A03; B05-B02A3; B05-C07; B06-D01; B06-F03; B07-A02; B07-D03; B07-D09; B10-A04; B10-A07; B10-A17; B10-B01B; B10-B02; B10-C04D; B14-G01

TECH

PHARMACEUTICALS - Preferred Composition: (I) further comprises 0.1-1.5 wt% of emulsifier (F), 0.1-1.0 wt% of stabilizer (G) and 0.005-0.2 wt% of additive (H). (A) is lyophilized antler powder. At least one (B) is alanine, arginine, asparigine, aspartic acid, cystine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine or valine. (I) also comprises at least one fatty acid (stearic acid, oleic acid, linoleic acid, lauric acid, caprylic acid, capric acid, myristic acid or palmitic acid). At least one (C) is starch, maltose, fructose, sucrose, glucose, sorbitol, arabinose, xylose, lactose, corn syrup solid, maltodextrins, dextrine or dextrose. At least one (D) is vitamin A, vitamin B1, vitamin B2, vitamin B6, vitamin B12, vitamin C, vitamin D, vitamin E, vitamin K, folic acid, biotin or pantothenic acid. At least one (E) is zinc, calcium, phosphorus, potassium, manganese, cobalt, iron, copper, sodium, magnesium, iodine, chlorine or fluorine. At least one (F) is mono- or diglyceride, sorbitan, monostearate, polysorbate 60, polysorbate 80, lecithin, emplex, caprol or myyerol. At least one (G) is xanthan gum, carboxymethylcellulose (CMC) gum, carageenan, Methocel (RTM; hydroxypropylmethylcellulose), Klucel (RTM; hydroxypropylcellulose), guar gum, locust bean gum, and alginates. At least one (H) is buffering agent (potassium phosphate and/or sodium phosphate), sequestrant (ethylenediamine tetra-acetic acid (EDTA), citric acid and/or polyphosphate), preservative (potassium propionate and/or potassium sorbate) or food pigment (Yellow No. 5, Yellow No. 6, Red No. 2, Red No. 40 or beta-carotene). (II) comprises (J), (K), (L) and (M) in the weight ratio 1:0.01:0.02:0.45-1:0.2:0.18:0.55. (J) is pharmaceutically acceptable beta-cyclodextrin, (K) is obtained by reacting 12-18C alcohol and 8-18C carboxylic acid, (L) is mucus proteinase inhibitor and (M) is propylene glycol.

ORGANIC CHEMISTRY - Preparation (claimed): Preparation of (I) comprises: (a) providing an antler extract mixture comprising 70-90 wt% of (A), 2-10 wt% of (B), 1-5 wt% of (C), 0.1-2 wt% of (D) and 0.1-3 wt% of (E); (b) adding 70-80 degrees C of pure water, 0.1-1.5 wt% of (F), 0.1-1.0 wt%

of (G) and 0.005-0.2 wt% of (H) to the powder mixture in a high speed blender, mixing well and heating at 50-70 degrees C for 10-20 minutes, in a powder mixture to water ratio of 1:15 -1:8;
(c) mixing the mixture well in a blender and heating it to 60-65 degrees C for 30 minutes;
(d) transferring the mixture thus obtained into a vacuum apparatus to degas;
(e) homogenizing the mixture under 1,000-1,500 psi pressure followed by a further pressure of 1,500-3,000 psi, followed by rapid chilling to 4 degrees C using a high-temperature short-time (HTST) chilling process; and
(f) transferring the product into a maturing vat, stirring gently at 4 degrees C for 12-24 hours to complete the degassing and maturing process.
Preparation of (A) comprises
(a) soaking velvet antlers in pure hot water at 80-90 degrees C for 30 minutes and separating the skin part from the other tissue part;
(b) homogenizing the skin part and tissue part separately;
(c) removing the hair portion from the homogenized skin part;
(d) recombining the homogenized skin part and the tissue part;
(e) separating the water-soluble and water-insoluble parts and pulverizing the water-insoluble part in a **fluidized bed** dryer and
drying the water-insoluble portion in an agitated swirl **fluidized bed** dryer; and
(f) pulverizing the water-soluble and water-insoluble parts into powder in a **fluidized bed** dryer at 75-90 degrees C.
Preparation of (II) comprises:
(a) mixing (J), (K), (L) and (M) and blending them with pure water at room temperature for 18-36 hours;
(b) adding (I) to the mixture thus obtained and blending at low speed at room temperature for 18-24 hours;
(c) incubating the mixture at 4 degrees C for 24-48 hours until **precipitate** performs;
(d) filtering the mixture to obtain the **precipitate** (II); and
(e) adding 3 fold of water to (II) and mixing well.
This is sterilized and packed with an aerosol suitable for nasal or sublingual delivery.

L109 ANSWER 26 OF 39 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-558442 [52] WPIX
CROSS REFERENCE: 2001-257830; 2004-051482
DOC. NO. CPI: C2003-150320 [52]
TITLE: Preparation of chewing gum tablet comprises mixing chewing gum powder with active composition having nutritional supplement to form nutritional supplement-containing powder
DERWENT CLASS: D13
INVENTOR: GUBLER S A
PATENT ASSIGNEE: (DESE-N) DESERET LAB INC
COUNTRY COUNT: 99

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 20030099741	A1	20030529	(200352)*	EN	6[0]	
US 6582738	B2	20030624	(200352)	EN		
WO 2003045160	A1	20030605	(200352)	EN		
AU 2002365385	A1	20030610	(200419)	EN		
EP 1458246	A1	20040922	(200462)	EN		
KR 2004053128	A	20040623	(200470)	KO		
BR 2002013016	A	20041005	(200475)	PT		

JP 2005510221	W	20050421	(200528)	JA 12	A23G003-30
CN 1575132	A	20050202	(200532)	ZH	A23G003-30
MX 2004004801	A1	20040901	(200553)	ES	
NZ 532172	A	20060127	(200612)	EN	
AU 2002365385	B2	20060824	(200708)	EN	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 20030099741	A1 CIP of	US 1999-394217	19990913
US 20030099741	A1	US 2001-995260	20011127
AU 2002365385	A1	AU 2002-365385	20021115
BR 2002013016	A	BR 2002-13016	20021115
CN 1575132	A	CN 2002-820857	20021115
EP 1458246	A1	EP 2002-803983	20021115
NZ 532172	A	NZ 2002-532172	20021115
WO 2003045160	A1	WO 2002-US36892	20021115
EP 1458246	A1	WO 2002-US36892	20021115
BR 2002013016	A	WO 2002-US36892	20021115
JP 2005510221	W	WO 2002-US36892	20021115
MX 2004004801	A1	WO 2002-US36892	20021115
NZ 532172	A	WO 2002-US36892	20021115
JP 2005510221	W	JP 2003-546672	20021115
KR 2004053128	A	KR 2004-703945	20040318
MX 2004004801	A1	MX 2004-4801	20040520
AU 2002365385	B2	AU 2002-365385	20021115

FILING DETAILS:

PATENT NO	KIND		PATENT NO	
US 20030099741	A1	CIP of	US 6322828	B
AU 2002365385	A1	Based on	WO 2003045160	A
EP 1458246	A1	Based on	WO 2003045160	A
BR 2002013016	A	Based on	WO 2003045160	A
JP 2005510221	W	Based on	WO 2003045160	A
MX 2004004801	A1	Based on	WO 2003045160	A
NZ 532172	A	Based on	WO 2003045160	A
AU 2002365385	B2	Based on	WO 2003045160	A

PRIORITY APPLN. INFO: US 2001-995260 20011127
US 1999-394217 19990913

INT. PATENT CLASSIF.:

MAIN: A23G003-30

SECONDARY: A23L001-30; A61K047-04; A61K009-20; A61K009-68

IPC ORIGINAL: A23G0004-00 [I,A]; A23G0004-00 [I,C]; A23G0004-02 [I,A]; A23G0004-02 [I,C]

IPC RECLASSIF.: A23G0004-00 [I,A]; A23G0004-00 [I,C]; A23G0004-02 [I,A]; A23G0004-02 [I,C]; A23G0004-04 [I,A]; A23G0007-00 [I,C]; A23G0007-02 [I,A]; A23L0001-30 [I,A]; A23L0001-30 [I,C]; A61K0047-02 [I,C]; A61K0047-04 [I,A]; A61K0009-00 [I,A]; A61K0009-00 [I,C]; A61K0009-20 [I,A]; A61K0009-20 [I,C]; A61K0009-20 [I,A]; A61K0009-20 [I,C]; A61K0009-68 [I,A]; A61K0009-68 [I,C]; A61K0009-68 [I,A]; A61K0009-68 [I,C]; H02P0005-00 [I,A]; H02P0005-00 [I,C]

BASIC ABSTRACT:

US 20030099741 A1 UPAB: 20060120

NOVELTY - Chewing gum tablet is prepared by cooling chewing gum composition, grinding cooled composition to form chewing gum powder, mixing chewing gum

powder with active composition having nutritional supplement to form nutritional supplement-containing powder, **granulating** nutritional supplement-containing powder, and forming nutritional supplement-containing **granules** into chewing gum tablet(s).

USE - For preparing chewing gum tablet.

ADVANTAGE - The invention results in chewing gum tablets that are precisely and uniformly formed in a well-defined shape and weight. It can be carried out in high-speed and efficient manufacturing facilities. MANUAL CODE: CPI: D03-E09

TECH

FOOD - Preferred Process: The cooling of the chewing gum composition comprises contacting the composition with coolant having reactive substance capable of cooling the composition to the brittle temperature. The grinding of cooled chewing gum composition is carried out in the presence of coolant. The chewing gum composition is mixed with solid carbon dioxide and anti-tacking agent. The chewing gum composition is cooled to temperature below -30degreesC. The **granulating** is carried out in fluid bed **granulator**. The preparation of chewing gum tablet further includes coating the nutritional supplement-containing powder in the fluid bed **granulator** with coating agent. The chewing gum powder is mixed with additive(s) prior to **granulation**.

Preferred Component: The coolant comprises carbon dioxide. The anti-tacking agent comprises **precipitated** silicon dioxide. The additives are from coating agents, binders, lubricants, or sweeteners. The nutritional supplement comprises vitamin(s), mineral nutrient(s), and herb(s). The vitamins are from vitamin A, vitamin C, vitamin D, vitamin E, vitamin K, vitamin B6, vitamin B12, thiamine, **riboflavin**, biotin, folic acid, niacin, and/or pantothenic **acid**. The **mineral** nutrients are from sodium, potassium, calcium, magnesium, phosphorus, sulfur, chlorine, iron, copper, iodine, zinc, selenium, manganese, chromium, molybdenum, fluorine, and/or cobalt.

Preferred Property: The nutritional supplement-containing **granules** have an average size of 15-30 mesh.

L109 ANSWER 27 OF 39 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-373742 [36] WPIX
CROSS REFERENCE: 2004-307041
DOC. NO. CPI: C2003-099523 [36]
TITLE: Partly-hydrolyzed fish gelatin useful as food additive or supplement, for e.g. the treatment of osteoporosis, alopecia and for preventive and curative treatment of tooth disease
DERWENT CLASS: B04; D13
INVENTOR: BONANOMI M; DE GREGORIO M; GREGORIO M D
PATENT ASSIGNEE: (BIOP-N) BIOPROGRESS SPA; (BONA-I) BONANOMI M; (GREG-I) GREGORIO M D
COUNTRY COUNT: 26

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
EP 1273239	A1	20030108	(200336)*	EN	11[0]	A23L001-0562
US 20040121949	A1	20040624	(200445)#	EN	7	A61K038-38
EP 1273239	B1	20040804	(200451)	EN		A23L001-0562
DE 60200861	E	20040909	(200459)	DE		
IT 1323390	B	20040816	(200547)	IT		A23B000-00
DE 60200861	T2	20050804	(200551)	DE		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 1273239 A1		EP 2002-425280	20020503
IT 1323390 B		IT 2001-RM380	20010702
DE 60200861 E		DE 2002-60200861	20020503
DE 60200861 T2		DE 2002-60200861	20020503
EP 1273239 B1		EP 2002-425280	20020503
DE 60200861 E		EP 2002-425280	20020503
DE 60200861 T2		EP 2002-425280	20020503
US 20040121949 A1		US 2002-324857	20021220
EP 1273239 B1	Related to	EP 2003-27512	20020503

FILING DETAILS:

PATENT NO	KIND	PATENT NO
DE 60200861 E	Based on	EP 1273239 A
DE 60200861 T2	Based on	EP 1273239 A
EP 1273239 B1	Related to	EP 1407677 A

PRIORITY APPLN. INFO: IT 2001-RM380 20010702
US 2002-324857 20021220

INT. PATENT CLASSIF.:

MAIN: A23B; A23L001-0562

IPC RECLASSIF.: A23J0003-00 [I,C]; A23J0003-06 [I,A]; A23J0003-34 [I,A]; A23L0001-05 [I,C]; A23L0001-0562 [I,A]; A23L0001-30 [I,A] ; A23L0001-30 [I,C]; A23L0001-302 [I,A]; A23L0001-302 [I,C]; A23L0001-303 [I,A]; A23L0001-304 [I,A]; A23L0001-304 [I,C]; A23L0001-305 [I,A]; A23L0001-305 [I,C]; A23L0002-385 [I,A]; A23L0002-385 [I,C]; A23L0002-52 [I,A]; A23L0002-52 [I,C]; A61K0038-01 [I,A]; A61K0038-01 [I,C]; A61K0038-39 [I,A]; A61K0038-39 [I,C]; A61P0019-00 [I,C]; A61P0019-10 [I,A]; C07K0014-435 [I,C]; C07K0014-46 [I,A]; C12P0021-06 [I,A]; C12P0021-06 [I,C]

BASIC ABSTRACT:

EP 1273239 A1 UPAB: 20060119

NOVELTY - A partly hydrolyzed fish gelatin (I) is used as food additive or supplement.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) use of (I) in the preparation of a medicament for the treatment of deficiency supply of amino acids, an increased consumption of amino acids or a defective absorption of amino acids in living organism;

(2) a composition comprising (I) useful as food additive and/or medicament; and

(3) a kit comprising a first container X holding a composition comprising vitamins and a second container Y holding (I). Both the containers are closed and the container X is disposed on container Y to join the contents of the container X into the container Y at the moment of use.

ACTIVITY - Osteopathic; Antiinflammatory; Anorectic. To two groups of eight rabbits on an empty stomach partly hydrolyzed fish gelatin (100 mg/kg) (test) and reference gelatin of bovine origin (100 mg/kg) (control) non-hydrolyzed with marked gelling properties at room temperature were administered. At predetermined times samples of blood from central artery of the ear were carried out to determine the plasma concentration of the free amino acids. The analysis was conducted after precipitation of plasma proteins. The standard errors were determined at 1 hour, 3 hours and at 6 hours. The result for the test/control was: 70.44/34.39 (at 1 hour); 36.21/17.74 (at 3 hours) and 22.86/32.85 (at 6 hours) respectively. The results showed that the absorption

of test evaluated in terms of free amino acids present in the blood was twice as compared to the control.
MECHANISM OF ACTION - None given.
USE - As food additive or supplement and/or medicament; in the preparation of a medicament for the treatment of deficiency supply of amino acids, increased consumption of amino acids or defective absorption of amino acids in living organism; in the treatment of osteoporosis, alopecia and trophism of the microcirculation and veins, parodontitis; for preventive and curative treatment of tooth disease connected with both thinning of the bony tissue and weakening of dental ligaments (claimed) and/or medical speciality; as an adjuvant in the treatment of convalescence, senescence, pregnancy, nursing, altered trophism of microcirculation and veins; and for treating obesity.
ADVANTAGE - (I) does not possess gelling property. (I) is devoid of inter-chain bonds between proteinic polymer chains constituting it. (I) does not contain sulfurized amino acids in free form; improves treatment acceptability by the patient avoiding the feeling of gastric swelling due to gelation; reduces the required doses for obtaining desired effects; allows the gelatin to be easily assimilable by the organism; allows use of lower dosage than that required if native gelatin were used; does not contain free sulfurized amino acids hence has no disagreeable aftertaste, which is typical of the previously used products; and reduces treatment cost. MANUAL CODE: CPI: B03-L; B04-N02; B11-C09; B14-C03; B14-E12; B14-N01;
B14-N06B; B14-R02; D03-H01C; D03-H01D; D03-H01J; D03-H01T2

TECH
ORGANIC CHEMISTRY - Preferred Composition: The composition comprises at least one e.g. vitamin A, vitamin B1, **vitamin B2**, vitamin B3, vitamin B6, vitamin C, vitamin D3, vitamin E or vitamin H. The composition further comprises at least one of amino **acid**, **mineral** salt, flavor, pH control, co-formulation aid or additive.
Preferred Gelatin: (I) has a molecular weight not exceeding 50000 Daltons and is water-soluble.
Preferred Kit: The container X holds a solubilizing liquids and the container Y holds the composition.

L109 ANSWER 28 OF 39 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-682871 [73] WPIX
DOC. NO. CPI: C2002-192704 [73]
TITLE: Composition of matter useful for treatment of e.g. mammalian cancer comprises aqueous alkali metal salt, especially cesium citrate and rubidium citrate
DERWENT CLASS: B05
INVENTOR: GILES B C
PATENT ASSIGNEE: (GILE-I) GILES B C
COUNTRY COUNT: 93

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2002069955	A1	20020912	(200273)*	EN	26[1]	A61K031-185
NO 2003003797	A	20031028	(200379)	NO		A61K033-14
EP 1372631	A1	20040102	(200409)	EN		A61K031-185
AU 2001239986	A1	20020919	(200433)	EN		
CN 1492758	A	20040428	(200447)	ZH	[0]	
JP 2004530659	W	20041007	(200466)	JA	43	A61K031-07
US 20050260277	A1	20051124	(200577)	EN		A61K038-23

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002069955	A1	WO 2001-US6672	20010228
AU 2001239986	A1	AU 2001-239986	20010228
CN 1492758	A	CN 2001-822926	20010228
EP 1372631	A1	EP 2001-914619	20010228
NO 2003003797	A	WO 2001-US6672	20010228
EP 1372631	A1	WO 2001-US6672	20010228
AU 2001239986	A1	WO 2001-US6672	20010228
CN 1492758	A	WO 2001-US6672	20010228
JP 2004530659	W	WO 2001-US6672	20010228
US 20050260277	A1	WO 2001-US6672	20010228
JP 2004530659	W	JP 2002-569131	20010228
NO 2003003797	A	NO 2003-3797	20030826
US 20050260277	A1	US 2003-469568	20030828

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1372631 A1	Based on	WO 2002069955 A
AU 2001239986 A1	Based on	WO 2002069955 A
JP 2004530659 W	Based on	WO 2002069955 A

PRIORITY APPLN. INFO: WO 2001-US6672 20010228
INT. PATENT CLASSIF.:
MAIN: A61K031-07; A61K031-185; A61K033-14
IPC RECLASSIF.: A61K0031-045 [I,C]; A61K0031-07 [I,A]; A61K0031-122 [I,A] ; A61K0031-122 [I,C]; A61K0031-185 [I,A]; A61K0031-185 [I,C]; A61K0031-19 [I,A]; A61K0031-191 [I,A]; A61K0031-194 [I,A]; A61K0031-198 [I,A]; A61K0031-21 [I,A] ; A61K0031-21 [I,C]; A61K0031-21 [I,C]; A61K0031-26 [I,A] ; A61K0031-35 [I,A]; A61K0031-35 [I,C]; A61K0031-375 [I,A]; A61K0031-375 [I,C]; A61K0031-4415 [I,A]; A61K0031-4415 [I,C]; A61K0031-455 [I,A]; A61K0031-455 [I,C]; A61K0031-4965 [I,A]; A61K0031-4965 [I,A]; A61K0031-4965 [I,C]; A61K0031-4965 [I,C]; A61K0031-568 [I,C]; A61K0031-5685 [I,A]; A61K0031-59 [I,A]; A61K0031-59 [I,A]; A61K0031-59 [I,C]; A61K0031-59 [I,C]; A61K0033-00 [I,A]; A61K0033-00 [I,C]; A61K0033-04 [I,A]; A61K0033-04 [I,C]; A61K0033-06 [I,A]; A61K0033-06 [I,C]; A61K0033-14 [I,A]; A61K0033-14 [I,C]; A61K0033-18 [I,A]; A61K0033-18 [I,C]; A61K0033-24 [I,A]; A61K0033-24 [I,C]; A61K0033-30 [I,A]; A61K0033-30 [I,C]; A61K0033-42 [I,A]; A61K0033-42 [I,C]; A61K0038-22 [I,A]; A61K0038-22 [I,C]; A61K0038-23 [I,A]; A61K0038-23 [I,C]; A61K0009-08 [I,A]; A61K0009-08 [I,C]; A61P0035-00 [I,A]; A61P0035-00 [I,C]; A61P0035-04 [I,A]; A61P0043-00 [I,A]; A61P0043-00 [I,C]

BASIC ABSTRACT:

WO 2002069955 A1 UPAB: 20060202

NOVELTY - A composition of matter comprises an aqueous alkali metal salt solution.

DETAILED DESCRIPTION - A composition of matter comprises an aqueous alkali metal salt solution. The alkali metal salt is of formula MA.

M = alkali metal selected from cesium and/or rubidium; A = chloride, sulfate, carbonate, phosphate, lactate, citrate or acetate.

MA dissociates in water to form M+ and A-. ACTIVITY - Cytostatic; Antitumor.

MECHANISM OF ACTION - None given.

USE - In the treatment of mammalian cancer (claimed). As the first selection for intervention, providing substantial pain reduction or elimination and

cancer remission, reserving costly testing and other therapies only for recalcitrant cancers. A test composition was orally administered to a patient as 4 ounces 2 times per 24 hours. The patient was monitored for stress and efficacy and also the therapy adjusted to obtain tumor remission and suppression response with minimal physiological stress. Failure to respond, either initially or after a period of favorable response, indicated the complementary or potentiating the ingredients.

ADVANTAGE - The composition can be formulated into a dry tablet or powdered capsule form for oral administration used for the long-term treatment of mammalian cancer. The composition monitors pH and adjusts the therapy so that the systemic pH, the tumor pHe and the tumor pHi fall within the predetermined range. The composition provides electro-negative charge, which reduces the excessive excitability of neurons, processes the stressful biological inflammatory complex such as supper oxides, peroxides, etc, thus normalizes and stabilizes the pHi and processes toxins. The composition provides a non-toxic drug, which can be administered to humans or other mammals suffering from cancer to increase pHe and pHi and to diminish systemic acidity and therapeutically treat metastatic tumors systemically and at the primary tumor site or sites with extremely low toxicity. The composition can function effectively as a stand-alone cancer treatment, such as surgical intervention, radiation or chemotherapy. The composition provides promotion of hydration of body fluids and stimulation of excretion of acidic toxins. The composition provides the active ingredient in a dosages that can be adjusted to fall within targeted pHi and pHe ranges providing a controllable degree of efficacy, so that malignant and non-malignant tumor stabilization and remission and elimination occurs in a predictable an gradual manner, avoiding the distress or mortality that can accompany tumor necrosis. The composition effectively stops the localized and systemic acidosis cycle, providing a fast-acting highly effective cost effective formulation for the therapeutically treatment of cancer and reduces the effective dose of active ingredients and provides maintenance of beneficial inter-cellular changes in the ionic environment.

MANUAL CODE: CPI: B01-D02; B02-B; B02-M; B02-N; B03-A; B03-E; B03-F; B03-G; B04-J04A; B05-A01A; B05-A01B; B05-A03A; B05-A03B; B05-B02A3; B05-B02C; B05-C04; B05-C05; B05-C07; B07-A02; B07-D04; B07-D10; B10-A09B; B10-C02; B10-C04; B12-M07; B14-H01B; B14-S12

TECH

PHARMACEUTICALS - Preferred Composition: The composition further comprises at least one substance

(a) to stimulate calcium accumulation (preferably selected from vitamin D, selenium salts, calcitonin or calcium ionophores);

(b) to reduce the elimination of sodium from cancer cells (preferably selected from monensin or sodium/potassium exchange inhibitors);

(c) pH-**modifying** substance (preferably selected from nigericin, amiloride, 4,4'-diisothioscyanostilbene 2,2-disulfonic acid or bifilomycin) to decrease acidity at the tumor site in the patient and systemic acidity in the patient;

(d) to depress glucose utilization by tumor cells;

(e) to increase the activation of apoptosis in the patient;

(f) that complements cesium and/or rubidium therapy by unrelated the ways including compounds known in the art and commonly used in chemotherapies that do not target ionic physiology; or

(g) to compensate for potassium loss due to any diuretic effect of the therapy (preferably selected from potassium, anti-oxidants, or mineral supplements including trace minerals).

Preferred Components: The alkali metal salt (200 mg - 10 g, preferably 250 - 2500 mg) is cesium citrate (400 mg) and/or rubidium citrate (100 mg). The solution further includes potassium salt (125 - 1000 mg), calcium (1250 mg), magnesium citrate (100 - 1250 mg), iodine, selenomethionine (50 - 150 mcg), vanadyl sulfate (1 - 5 mcg), zinc gluconate (25 - 100 mg), Vitamin D (1000 - 2000 IU), vitamin A (1000 - 2500 IU), buffered vitamin C

(L-ascorbic acid) (500 - 2500 mg), malic acid (50 - 250 mg), COq (12.5 - 25 mg), DHEA (dehydroepiandrosterone) (2.5 - 25 mg), B3 methyl nicotinate (10 - 15 mg), B6 (12.5 - 50 mg), or B12 (10 - 25 mg). The potassium salt is selected from potassium phosphate, potassium gluconate, or potassium acetate. The solution is buffered and isotonic to blood.

L109 ANSWER 29 OF 39 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-331086 [29] WPIX
DOC. NO. CPI: C2000-100370 [29]
TITLE: Compositions for enhancing the penetration of topical skin agents into the skin comprises hydrophobic- and/or hydrophilic active agent(s) and a polymeric emulsifier
DERWENT CLASS: A96; B05; D21; P34; P41
INVENTOR: KUNG J; LIU J; LIU J C; NIEMIEC S; NIEMIEC S M
PATENT ASSIGNEE: (JOHJ-C) JOHNSON & JOHNSON; (JOHJ-C) JOHNSON & JOHNSON CONSUMER CO INC; (KUNG-I) KUNG J; (LIUJ-I) LIU J; (NIEM-I) NIEMIEC S
COUNTRY COUNT: 35

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
EP 998914	A1	20000510	(200029)*	EN	12[0]	A61K007-48
AU 9953544	A	20000420	(200029)	EN		A61K007-48
JP 2000143493	A	20000523	(200033)	JA	11	A61K007-48
CA 2285818	A1	20000413	(200037)	EN		A61K007-48
CN 1253022	A	20000517	(200041)	ZH		A61K047-32
BR 9904719	A	20001128	(200067)	PT		
KR 2000029011	A	20000525	(200110)	KO		
ZA 9906444	A	20010627	(200140)	EN	26	A61K000-00
MX 9909325	A1	20010101	(200166)	ES		B02C023-18
US 20010031281	A1	20011018	(200166)	EN		A61K009-14
US 20020006418	A1	20020117	(200212)	EN		A61K007-42
US 20020064560	A1	20020530	(200240)	EN		A61K035-78
US 20030219392	A1	20031127	(200378)	EN		A61K007-42
AU 2004203072	A1	20040805	(200473)#	EN		A61K007-48
TW 592714	A	20040621	(200506)	ZH		A61K007-02

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 998914 A1		EP 1999-308012	19991012
US 20010031281 A1	Provisional	US 1998-104060P	19981013
US 20020006418 A1	Provisional	US 1998-104060P	19981013
US 20020064560 A1	Provisional	US 1998-104060P	19981013
US 20030219392 A1	Provisional	US 1998-104060P	19981013
US 20010031281 A1	Cont of	US 1999-361426	19990727
US 20020006418 A1		US 1999-361426	19990727
US 20020064560 A1	Cont of	US 1999-361426	19990727
US 20030219392 A1	Cont of	US 1999-361426	19990727
AU 9953544 A		AU 1999-53544	19991008
AU 2004203072 A1	Div Ex	AU 1999-53544	19991008
MX 9909325 A1		MX 1999-9325	19991011
CA 2285818 A1		CA 1999-2285818	19991012
JP 2000143493 A		JP 1999-290018	19991012
KR 2000029011 A		KR 1999-44087	19991012
ZA 9906444 A		ZA 1999-6444	19991012
BR 9904719 A		BR 1999-4719	19991013

CN 1253022 A	CN 1999-121545 19991013
TW 592714 A	TW 1999-117641 19991103
US 20010031281 A1	US 2001-819545 20010328
US 20020064560 A1	US 2001-20623 20011207
US 20030219392 A1	US 2003-414751 20030416
AU 2004203072 A1	AU 2004-203072 20040707

PRIORITY APPLN. INFO: US 1999-361426 19990727
US 1998-104060P 19981013
US 2001-819545 20010328
US 2001-20623 20011207
US 2003-414751 20030416
AU 2004-203072 20040707

INT. PATENT CLASSIF.:
MAIN: A61K007-02; B02C023-18
IPC RECLASSIF.: A01N0031-00 [I,C]; A01N0031-04 [I,A]; A61K [I,S]; A61K0031-045 [I,C]; A61K0031-07 [I,A]; A61K0031-519 [I,C] ; A61K0031-525 [I,A]; A61K0031-59 [I,A]; A61K0031-59 [I,C]; A61K0031-70 [I,A]; A61K0031-70 [I,C]; A61K0031-7004 [I,A]; A61K0031-7004 [I,C]; A61K0045-00 [I,C]; A61K0045-08 [I,A]; A61K0047-32 [I,A]; A61K0047-32 [I,C]; A61K0006-00 [I,A]; A61K0006-00 [I,C]; A61K0008-00 [I,A]; A61K0008-00 [I,C]; A61K0009-14 [I,A]; A61K0009-14 [I,C]; A61M0037-00 [I,A]; A61M0037-00 [I,C]; A61Q0017-00 [I,A]; A61Q0017-00 [I,C]; A61Q0019-00 [I,A]; A61Q0019-00 [I,C]; H04B0007-185 [I,A]; H04B0007-185 [I,C]

BASIC ABSTRACT:

EP 998914 A1 UPAB: 20050830

NOVELTY - Compositions for enhancing the penetration of topical skin agents into the epidermal and dermal layers of the skin comprise at least one active ingredient which is hydrophilic or hydrophobic, a polymeric emulsifier and, alternatively, a sugar or a polyoxyethylene alcohol.

DETAILED DESCRIPTION - Composition comprises an active agent selected from hydrophobic- and hydrophilic active agents and their combination and a polymeric emulsifier. ACTIVITY - Antimicrobial; antiallergic; dermatological; analgesic; antiinflammatory.

USE - As topical compositions for delivery of active agents. The active agents include pharmaceuticals, or cosmetic nutrients or skin conditioners.

ADVANTAGE - The compositions enhance the penetration of hydrophobic or hydrophilic topical active agents through the outermost layer of the skin and also regulate the penetration of such agents. The compositions are mild and non-irritating despite the increased penetration of topical active agents. Penetration studies were conducted using human cadaver skin sections and retinol as a lipophilic active agent and ascorbic acid 2-glucoside (AA2G) as a hydrophilic agent. A control formulation (A) containing a conventional emulsifier and only cetearyl glucoside delivered only 0.175% of the applied dose of retinol into the epidermis. When a formulation (B) containing hydrophobically **modified** acrylic acid emulsifier was used, the percentage of retinol increased to 0.642%, a 3.669 fold increase in delivery. When AA2G and cetearyl glucoside were placed into formulation (C) with retinol, the retinol permeation increased to 0.241%, a 1.38-fold increase over the control formulation (A). Formulation (D) containing both hydrophobically modified acrylic acid and AA2G gave a total delivery of retinol of 1.26%, a 7.2-fold increase in retinol delivery to the epidermis. Formulation (E) containing hydrophobically modified acrylic acid, polyoxyethylene alcohol and AA2G demonstrated that the addition of polyoxyethylene alcohol increased the penetration of AA2G from 0.18 (in D) to 1.016%, which is a 5.65-fold increase of delivery of AA2G. The retinol permeation decreased from 1.25 (in D) to 0.464% in (E), which was a 0.36-fold decrease. This proved that the novel compositions afford a method of regulating the delivery of both hydrophilic and lipophilic agents. MANUAL CODE: CPI: A04-F06E5; A05-H03; A12-V01; B03-L; B04-A10;

B04-C03B; B04-C03C; B06-H; B10-A07; B10-A22; B10-B02; B12-M02F; B14-A01; B14-C03; B14-C08; B14-E05; B14-F02C; B14-F02D; B14-G02A; B14-K01; B14-K01B; B14-L06; B14-L09; B14-N17; B14-R04; B14-S08; D08-B09A

TECH

POLYMERS - The composition further comprises a hydrophobically-modified hydrophilic polymer which is preferably a hydrophobically-modified acrylate, especially 10-30C alkyl acrylate cross-polymer. The composition further comprises a polyoxyalkylene alcohol, preferably polyoxyethylene alcohol.

ORGANIC CHEMISTRY - The composition further comprises a sugar.

PHARMACEUTICALS - The hydrophobic and hydrophilic active agents are selected from antimicrobials, allergy inhibitors, anti-acne, analgesics, antitussives, antipruritics, anesthetics, antihistamines, anti-infective agents, inflammation inhibitors, antiemetics, anticholinergics, vasoconstrictors, vasodilators, wound healing promoters, vitamin B complex, pro-vitamins, amino acids and their derivatives, herbal extracts, retinoids, flavanoids, anti-oxidants, anti-inflammatory, skin conditioners, skin lighteners, chelating agents, cell turnover enhancers, coloring agents, fragrances, pigments and sunscreens.

L109 ANSWER 30 OF 39 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-294952 [26] WPIX
DOC. NO. CPI: C2000-089308 [26]
TITLE: Purification and crystallization of **riboflavin** to give more soluble form suitable for pharmaceutical or foodstuff use, by activated carbon treatment in acid solution, cross-flow filtration and precipitation
DERWENT CLASS: B02; D13; E13
INVENTOR: WAGNER G
PATENT ASSIGNEE: (HOFF-C) HOFFMANN LA ROCHE & CO AG F; (HOFF-C) ROCHE VITAMINS INC; (STAM-C) DSM IP ASSETS BV
COUNTRY COUNT: 31

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
EP 995749	A1	20000426	(200026)*	DE	9[0]	
JP 2000128880	A	20000509	(200032)	JA	5	
CN 1251365	A	20000426	(200036)	ZH		C07D475-14
CA 2282908	A1	20000419	(200037)	EN		
BR 9905331	A	20000815	(200045)	PT		
US 6150364	A	20001121	(200101)	EN		
KR 2000029132	A	20000525	(200110)	KO		
CN 1117752	C	20030813	(200549)	ZH		C07D475-14
EP 995749	B1	20070307	(200720)	DE		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 995749	A1	EP 1999-120364	19991013
CA 2282908	A1	CA 1999-2282908	19990920
CN 1251365	A	CN 1999-121368	19991012
CN 1117752	C	CN 1999-121368	19991012
JP 2000128880	A	JP 1999-293063	19991015
KR 2000029132	A	KR 1999-44908	19991016
BR 9905331	A	BR 1999-5331	19991018
US 6150364	A	US 1999-420824	19991019

PRIORITY APPLN. INFO: EP 1998-119686 19981019
INT. PATENT CLASSIF.:
IPC ORIGINAL: C07D0475-00 [I,C]; C07D0475-14 [I,A]
IPC RECLASSIF.: A61K0031-519 [I,A]; A61K0031-519 [I,C]; A61K0031-525 [I,A]; C07D0475-00 [I,C]; C07D0475-14 [I,A]
BASIC ABSTRACT:
EP 995749 A1 UPAB: 20060116
NOVELTY - Purification and crystallization of **riboflavin** to give more soluble form suitable for pharmaceutical or foodstuff use, by activated carbon treatment in acid solution, cross-flow filtration and precipitation.
DETAILED DESCRIPTION - Purification and crystallization of **riboflavin** (I) involves:
(i) dissolving acicular (I) of stable modification A in aqueous mineral acid with thorough mixing at 30degreesC or less; (ii) adding activated carbon; (iii) removing the carbon (plus adsorbed impurities) by cross-flow filtration via a ceramic membrane of pore size 20-200 nm; (iv) treating the filtrate with a 5-10 fold volume of water at 30degreesC or less; and
(v) recovering the precipitated spherical crystals of (I) by centrifugation or filtration.
ACTIVITY - None given.
MECHANISM OF ACTION - None given.
USE - The process is useful for converting synthetically or biotechnologically prepared (I) into a form suitable for use in pharmaceuticals or foodstuffs.
ADVANTAGE - The product has purity at least 98%. It is in the form of spherical crystals having an irregular surface (i.e. the **B** or **C modification**), having higher surface, superior physical properties (e.g. flow and dissolution properties, abrasion resistance and tableting characteristics) and increased bioavailability compared with the starting material. MANUAL CODE: CPI: **B03-C**; D03-H; E06-D17

Member(0002)
ABEQ JP 2000128880 A UPAB 20060116
NOVELTY - Purification and crystallization of **riboflavin** to give more soluble form suitable for pharmaceutical or foodstuff use, by activated carbon treatment in acid solution, cross-flow filtration and precipitation.
DETAILED DESCRIPTION - Purification and crystallization of **riboflavin** (I) involves:
(i) dissolving acicular (I) of stable modification A in aqueous mineral acid with thorough mixing at 30degreesC or less;
(ii) adding activated carbon;
(iii) removing the carbon (plus adsorbed impurities) by cross-flow filtration via a ceramic membrane of pore size 20-200 nm;
(iv) treating the filtrate with a 5-10 fold volume of water at 30degreesC or less; and
(v) recovering the precipitated spherical crystals of (I) by centrifugation or filtration.
ACTIVITY - None given.
MECHANISM OF ACTION - None given.
USE - The process is useful for converting synthetically or biotechnologically prepared (I) into a form suitable for use in pharmaceuticals or foodstuffs.
ADVANTAGE - The product has purity at least 98%. It is in the form of spherical crystals having an irregular surface (i.e. the **B** or **C modification**), having higher surface, superior physical properties (e.g. flow and dissolution properties, abrasion resistance and tableting characteristics) and increased bioavailability compared with the starting material.

Member(0003)
ABEQ CN 1251365 A UPAB 20060116
NOVELTY - Purification and crystallization of **riboflavin** to give more soluble form suitable for pharmaceutical or foodstuff use, by activated carbon treatment in acid solution, cross-flow filtration and precipitation.
DETAILED DESCRIPTION - Purification and crystallization of **riboflavin** (I) involves:
(i) dissolving acicular (I) of stable modification A in aqueous mineral acid with thorough mixing at 30degreesC or less;
(ii) adding activated carbon;
(iii) removing the carbon (plus adsorbed impurities) by cross-flow filtration via a ceramic membrane of pore size 20-200 nm;
(iv) treating the filtrate with a 5-10 fold volume of water at 30degreesC or less; and
(v) recovering the precipitated spherical crystals of (I) by centrifugation or filtration.
ACTIVITY - None given.
MECHANISM OF ACTION - None given.
USE - The process is useful for converting synthetically or biotechnologically prepared (I) into a form suitable for use in pharmaceuticals or foodstuffs.
ADVANTAGE - The product has purity at least 98%. It is in the form of spherical crystals having an irregular surface (i.e. the **B** or **C modification**), having higher surface, superior physical properties (e.g. flow and dissolution properties, abrasion resistance and tableting characteristics) and increased bioavailability compared with the starting material.

Member(0006)
ABEQ US 6150364 A UPAB 20060116
NOVELTY - Purification and crystallization of **riboflavin** to give more soluble form suitable for pharmaceutical or foodstuff use, by activated carbon treatment in acid solution, cross-flow filtration and precipitation.
DETAILED DESCRIPTION - Purification and crystallization of **riboflavin** (I) involves:
(i) dissolving acicular (I) of stable modification A in aqueous mineral acid with thorough mixing at 30degreesC or less;
(ii) adding activated carbon;
(iii) removing the carbon (plus adsorbed impurities) by cross-flow filtration via a ceramic membrane of pore size 20-200 nm;
(iv) treating the filtrate with a 5-10 fold volume of water at 30degreesC or less; and
(v) recovering the precipitated spherical crystals of (I) by centrifugation or filtration.
ACTIVITY - None given.
MECHANISM OF ACTION - None given.
USE - The process is useful for converting synthetically or biotechnologically prepared (I) into a form suitable for use in pharmaceuticals or foodstuffs.
ADVANTAGE - The product has purity at least 98%. It is in the form of spherical crystals having an irregular surface (i.e. the **B** or **C modification**), having higher surface, superior physical properties (e.g. flow and dissolution properties, abrasion resistance and tableting characteristics) and increased bioavailability compared with the starting material.
TECH
ORGANIC CHEMISTRY - Preferred Process: Step (i) is carried out using nitric or especially hydrochloric acid, at 5-25 (preferably

10-20)degreesC. In step (ii) activated carbon of bulk density 250-400 (preferably 300) kg/m3, specific surface 1200-1600 (preferably 1400) m2/g and average particle size 20-70 mum is used at 0.5-9 (preferably 3) wt. % based on the (I) content, optionally in combination with a filter aid. In step (iii) the membrane has pore size ca. 50 nm. In step (iv) crystallization is carried out at 4-10degreesC. Preferably the process is carried out continuously, with a dwell time in the crystallizer in step (iv) of 5-25 (especially 10-13) minutes. The spherical crystals of (I) are collected on a band filter, washed with water and dried.

L109 ANSWER 31 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2007:62712 USPATFULL Full-text
TITLE: Mixtures of polypeptides, compositions containing and processes for preparing same, and uses thereof
INVENTOR(S): Pinchasi, Irit, Ra'anana, ISRAEL
Dolitzky, Ben-Zion, Petach-Tikva, ISRAEL
Frenkel, Anton, Modiin, ISRAEL
Schwartz, Michal, Rehovot, ISRAEL
Arnon, Ruth, Rehovot, ISRAEL
Aharoni, Rina, Rehovot, ISRAEL
PATENT ASSIGNEE(S): Yeda Research and Development Co. Ltd. (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2007054857	A1	20070308
APPLICATION INFO.:	US 2006-541263	A1	20060929 (11)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2005-223408, filed on 9 Sep 2005, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2004-608844P	20040909 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: COOPER & DUNHAM, LLP, 1185 AVENUE OF THE AMERICAS, NEW YORK, NY, 10036, US
NUMBER OF CLAIMS: 32
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 31 Drawing Page(s)
LINE COUNT: 3755
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides a composition comprising a mixture of polypeptides, wherein each polypeptide (a) is a copolymer of the amino acids L-glutamic acid, L-alanine, L-tyrosine, and L-lysine, and (b) may be in the form of a pharmaceutically acceptable salt; and wherein in the mixture (i) the polypeptides have an average molecular weight in the range 13,500 to 18,500 daltons, (ii) 13% to 38% of the polypeptides have a diethylamide group instead of a carboxyl group present at one end thereof, and (iii) 68% of the polypeptides have a molecular weight between 7,000 and 41,000 daltons. In an embodiment, the average molecular weight is 16,000 daltons, and processes for preparing and its uses.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD The invention includes salts of the polypeptide mixture of the invention. As used herein, the term "salts" refers to both salts of

carboxyl groups and to acid addition salts of amino groups of the peptide molecule. Salts of a carboxyl group may be formed by means well known in the art and include inorganic salts, for example, sodium, calcium, ammonium, ferric or zinc salts, and the like, and salts with organic bases such as those formed for example, with amines, such as triethanolamine, arginine, or lysine, piperidine, procaine, and the like. Acid addition salts include, for example, salts with **mineral acids** such as, for example, hydrochloric acid or sulfuric acid, and salts with organic acids, such as, for example, acetic acid, citric acid or trifluoroacetic acid. Such salts are preferably used to modify the pharmaceutical properties of the peptide insofar as stability, solubility, etc., are concerned.

DETD Fourier Transformed Infra Red Spectrum (FTIR) Spectrum of the Polypeptide Mixture of the Invention (RS)

TABLE 4

IR absorption maxima of a 1% dispersion of the polypeptide mixture of the invention in KBr

Absorption (cm.sup.-1)	Assignment
1655.0	C.dbd.O stretching (amide I)
1550.6	N--H in-plane bending **modified** by C--N stretch
1406.0	CO2" symmetric vibration
1248.1	C--N stretching mode modified by N--H in-plane bending (amide III)

DETD Determination of molecular weights (MW) distribution in the polypeptide mixture of the invention by SEC-chromatography requires a suitable set of MW markers. As the polypeptide mixture of the invention differs from native protein, no commercial protein MW markers could be used for this purpose and markers related to the mixture of polypeptides of the invention ("polypeptide markers") had to be produced. In order to obtain marker set for MW calibration curve, five markers were designed with MW range from about 16,000 Da to 27,000 Da (table 6). The polypeptide markers were produced by recombinant methods. The markers cDNA were sub-cloned into pET-21a vector (Merck cat# 69740) and cloned into HMS174(DE3) E. coli strain (Merck cat# 69453). After expression, two **precipitations** and two chromatography steps gave the markers in at least 80% purity.

DETD Following copolymerization, process water is added and the protected polypeptides are subjected to **precipitation**, chopping, and dispersion for 1.25 hours. The protected polypeptides are then subjected to filtration and washing. The filter-cake is dried in a vacuum at 60° C.±5° C. at a pressure of less than 20 mmHg for 12 hours, and then subjected to milling. This yields a mixture of protected polypeptides, wherein the side chain functional groups of two amino acids (glutamic acid and lysine) are protected to avoid cross-linking.

IT 50-02-2, Dexamethasone 50-18-0, Cyclophosphamide 50-23-7, Hydrocortisone 50-24-8, Prednisolone 50-44-2, 6-Mercaptopurine 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 50-53-3, biological studies 50-55-5, Reserpine 50-81-7, Vitamin C, biological studies 51-34-3, Scopolamine 51-43-4, Epinephrine 51-55-8, Atropine, biological studies 51-83-2, Carbachol 51-85-4, Cystamine 52-86-8, Haloperidol 53-03-2, Prednisone 54-85-3, Isoniazide 54-96-6, 3,4-Diaminopyridine 55-91-4, Isoflurophate 56-81-5, Glycerin, biological studies 56-94-0 57-00-1, Creatine 57-41-0, Phenytoin 58-38-8 58-73-1, Diphenhydramine 58-74-2, Papaverine 59-05-2, Methotrexate 59-30-3, Folic acid, biological

studies 59-66-5, Acetazolamide 59-96-1, Phenoxybenzamine 67-20-9, Nitrofurantoin 68-88-2, Hydroxyzine 72-69-5, Nortriptyline 74-79-3, L-Arginine, biological studies 76-57-3, Codeine 79-43-6, biological studies **83-88-5**, Riboflavin, biological studies 89-57-6, 5-Aminosalicylic acid 92-13-7, Pilocarpine 92-84-2, Phenothiazine 94-78-0, Phenazopyridine 98-92-0, Nicotinamide 99-20-7, Trehalose 100-97-0, Methenamine, biological studies 101-31-5, Hyoscyamine 113-53-1, Dothiepin 125-33-7, Primidone 130-95-0, Quinine 155-09-9, Tranylcypromine 298-46-4, Carbamazepine 298-50-0, Propantheline 302-79-4, Retinoic acid 303-98-0, Coenzyme Q10 438-60-8, Protriptyline 439-14-5, Diazepam 443-48-1, Metronidazole 446-86-6, Azathioprine 495-40-9D, Butyrophenone, derivs. 504-24-5, 4-Aminopyridine 523-87-5, Dimenhydrinate 541-15-1, Carnitine 569-65-3, Meclizine 578-68-7D, 4-Aminoquinoline, derivs. 599-79-1, Sulfasalazine 603-50-9, Bisacodyl 745-65-3, Alprostadil 768-94-5, Amantadine 846-50-4, Temazepam 915-30-0, Diphenoxylate 1134-47-0, Baclofen 1200-22-2, Lipoic acid 1309-42-8, Magnesium hydroxide 1406-16-2D, Vitamin D, derivs. 1406-18-4, Vitamin E 1622-61-3, Clonazepam 1668-19-5, Doxepin 2152-34-3, Pemoline 4205-90-7, Clonidine 4291-63-8, Cladribine 5633-20-5, Oxybutynin 6493-05-6, Pentoxifylline 7601-54-9, Sodium phosphate 7782-49-2, Selenium, biological studies 8063-16-9, Psyllium mucilloid 10041-19-7, Docusate 10118-90-8, Minocycline 11000-17-2, Vasopressin 11103-57-4, Vitamin A 14605-22-2, Tauroursodeoxycholic acid 14663-23-1, Dantrolene sodium 15722-48-2, Olsalazine 16679-58-6, Desmopressin 18378-89-7, Mithramycin 19794-93-5, Trazodone 19982-08-2, Memantine 22664-55-7, Metipranolol 23047-25-8, Lofepramine 26921-17-5, Timolol maleate 28981-97-7, Alprazolam 30562-34-6, Geldanamycin 32222-06-3, Calcitriol 34911-55-2, Bupropion 36505-84-7, Buspirone 41294-56-8, Alphacalcidol 47141-42-4, Levobunolol 51322-75-9, Tizanidine 51781-06-7, Carteolol 52365-63-6, Dipivefrin 53123-88-9, Rapamycin 53179-11-6, Loperamide 54910-89-3, Fluoxetine 57308-51-7, Carbidopa-levodopa mixture 59277-89-3, Acyclovir 59729-33-8, Citalopram 59803-98-4, Brimonidine 59865-13-3, Cyclosporine 60142-96-3, Gabapentin 61869-08-7, Paroxetine 63590-64-7, Terazosin 63659-18-7, Betaxolol 65271-80-9, Mitoxantrone 66711-21-5, Apraclonidine 68291-97-4, Zonisamide 68693-11-8, Modafinil 71320-77-9, Moclobemide 79617-96-2, Sertraline 79902-63-9, Simvastatin 80573-04-2, Balsalazide 82626-48-0, Zolpidem 83366-66-9, Nefazodone 84057-84-1, Lamotrigine 85650-52-8, Mirtazapine 85721-33-1, Ciprofloxacin 91524-16-2, Timolol hemihydrate 93413-69-5, Venlafaxine 97240-79-4, Topiramate 107231-12-9, Botulinum toxin 107452-89-1, Ziconotide 119431-25-3, Eliprodil 120279-96-1, Dorzolamide 124937-51-5, Tolterodine 128298-28-2, Remacemide 130209-82-4, Latanoprost 136236-51-6, Rasagiline 138890-62-7, Brinzolamide 139755-83-2, Sildenafil 148553-50-8, Pregabalin 155206-00-1, Bimatoprost 157283-68-6, Travoprost 189261-10-7, Natalizumab 216503-57-0, Alemtuzumab 248281-84-7, Laquinimod
(therapeutic combinations containing mixts. of polypeptides comprising alanine, glutamic acid, lysine and tyrosine)

L109 ANSWER 32 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2006:281172 USPATFULL Full-text
TITLE: Process for the purification of riboflavin
INVENTOR(S): Gloor, Arnold, Oberwil, SWITZERLAND

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2006240112	A1	20061026	
APPLICATION INFO.:	US 2004-565443	A1	20040720	(10)

	WO 2004-EP8097	20040720
		20060512 PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	EP 2003-16512	20030722

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Stephen M Haracz, Bryan Cave, 1290 Avenue of the Americas, New York, NY, 10104-3300, US
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Page(s)
LINE COUNT: 1046
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to a process for the purification of riboflavin comprising the steps of (a) **precipitating** a first crystalline form of riboflavin, (b) isolating the first crystalline form of riboflavin, (c) transforming the first crystalline form of riboflavin into a second crystalline form of riboflavin under conditions that decompose diluted DNA, and (d) isolating the second crystalline form of riboflavin, provided that at ambient temperature the first crystalline form of riboflavin is thermodynamically less stable than the second crystalline form of riboflavin.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to a process for the purification of riboflavin comprising the steps of (a) **precipitating** a first crystalline form of riboflavin, (b) isolating the first crystalline form of riboflavin, (c) transforming the first crystalline form of riboflavin into a second crystalline form of riboflavin under conditions that decompose diluted DNA, and (d) isolating the second crystalline form of riboflavin, provided that at ambient temperature the first crystalline form of riboflavin is thermodynamically less stable than the second crystalline form of riboflavin.

SUMM In the purification step (third step) lipids, proteins, DNA and other organic and inorganic compounds may be removed to a certain extent only. It has been reported that a purity of up to 97 wt.-% can be achieved by adding 2 wt.-% of sulfuric **acid** or another **mineral acid** and heating the reaction slurry to a temperature in the range of 95° C. to 105° C.

SUMM This underlying technical problem has been solved by the subject matter of the patent claims, i.e. by a process for the purification of riboflavin comprising the steps of

(a) **precipitating** a first crystalline form of riboflavin,
(b) isolating the first crystalline form of riboflavin,
(c) transforming the first crystalline form of riboflavin into a second crystalline form of riboflavin under conditions that decompose diluted DNA, and
(d) isolating the second crystalline form of riboflavin, provided that at ambient temperature the first crystalline form of riboflavin is thermodynamically less stable than the second crystalline form of riboflavin.

SUMM The invention is based on the unexpected finding that, depending on the conditions in the fermenter, the crystallization of riboflavin during fermentation leads to different crystalline forms (modifications). The

analysis of the riboflavin crystals in the fermentation broth revealed that in some batches an anhydrate (i.e. riboflavin anhydrate I) and in other batches a hydrate (i.e. riboflavin dihydrate) was **precipitated.** In other batches mixtures of both crystalline forms were found. Even a third crystalline form (i.e. riboflavin tetrahydrate) was identified in some cases. These crystalline forms, i.e. riboflavin hydrates and riboflavin anhydrates were characterized by X-ray powder diffraction (XRD) and Dynamic Vapor Sorption (DVS). The solubilities of the different crystalline forms were investigated by Raman spectroscopy. The combination of DVS with XRD allows to investigate the formation of the hydrates.

SUMM As in the prior art the nomenclature of the forms (modifications) of crystalline riboflavin is not unitary, the different terms are summarized in the table here below:

nomenclature in this specification crystalline form of riboflavin	nomenclature of the prior art EP-A 995 749	U.S. Pat. No. 2,324,800	U.S. Pat. No. 2,603,633	U.S. Pat. No. 2,797,215	U.S. Pat. No. 4,687,847	FIG.
anhydrate I	modification A	=type A	type A	=type A	A	type A
anhydrate II	--	--	--	--	B	--
anhydrate III	--	--	--	--	C	--
monohydrate	**modification B/C**	--	--	--	D	--
dihydrate	--	--	--	--	E	--
tetrahydrate	--	--	type C	--	F	type C
anhydrate II + monohydrate			type B			type B

SUMM In step (a) of the process according to the invention a first crystalline form of riboflavin is **precipitated**, i.e. crystallized. Preferably step (a) is performed starting from the crude reaction slurry produced by microorganisms in a fermenter (fermentation broth). Suitable microorganisms include non genetically modified organisms (non GMO) and genetically modified organisms (GMO). The fermentation process may be carried out continuously or as a batch process, the latter being preferred. Usually the amount of water contained in the fermenter is not sufficient to keep the entire amount of the riboflavin product dissolved. Thus, only the amount of riboflavin obtained in the very beginning of the fermentation process stays in solution, but in the course of the progressing fermentation, when a certain level of supersaturation has been reached, the riboflavin spontaneously starts to crystallize. In general, the crystallization initiates well in advance of the termination of the fermentation process. Therefore, at the end of the process the majority of the product has been **precipitated** in form of crystalline riboflavin (first crystalline form of riboflavin) and only a comparably

small amount of riboflavin remains in solution.

SUMM On the one hand it has to be prevented that the crystalline form of riboflavin, which is **precipitated** in step (a), is thermodynamically the most stable form of crystalline riboflavin at ambient temperature, as in that case no transformation would be possible into any second crystalline form being thermodynamically more stable at ambient temperature. On the other hand the first crystalline form of riboflavin should be obtainable upon controlled **precipitation** and should stand the conditions of fermentation and an optional consecutive pasteurization step. Any crystalline form that exhibits these properties enables an efficient purification of riboflavin, particularly a significant decrease of the DNA concentration contained in the riboflavin crystals in step (c).

SUMM In a preferred embodiment of the process according to the invention the first crystalline form of riboflavin **precipitated** in step (a) comprises a riboflavin hydrate, preferably riboflavin monohydrate, riboflavin dihydrate or riboflavin tetrahydrate. Most preferably, the first crystalline form of riboflavin **precipitated** in step (a) is riboflavin dihydrate.

SUMM Depending on the reaction conditions in step (a), the first crystalline form of riboflavin which spontaneously **precipitates** from the fermentation broth is not necessarily the desired first crystalline form of riboflavin. Thus, it may become necessary to control the form of the **precipitate** of crystalline riboflavin which is **precipitated** in step (a), i.e. preferably produced In the course of the fermentation process.

SUMM It has been surprisingly found that in step (a) the formation of the desired first crystalline form of riboflavin in the fermenter can be controlled by initiation of the crystallization by means of seed crystals having a certain crystalline structure. The addition of suitable seed crystals to the fermentation broth causes the **precipitation** of a distinct first crystalline form of riboflavin. Therefore, the **precipitation** of the preferred first crystalline form of riboflavin (e.g. riboflavin monohydrate, riboflavin dihydrate or riboflavin tetrahydrate), preferably riboflavin dihydrate can be performed by means of selected suitable seed crystals.

SUMM In a preferred embodiment of the process according to the invention the **precipitation** of the first crystalline form of riboflavin in step (a) is initiated by means of seed crystals, preferably by means of seed crystals of riboflavin. Preferably the seed crystals comprise seed crystals of a riboflavin hydrate, more preferably of riboflavin monohydrate, riboflavin dihydrate or riboflavin tetrahydrate. Most preferably the seed crystals of riboflavin comprise riboflavin monohydrate.

SUMM Preferably the first crystalline form of riboflavin **precipitated** in step (a) is riboflavin dihydrate or riboflavin tetrahydrate which is obtained by means of suitable seed crystals. Preferably the first crystalline form of riboflavin is riboflavin dihydrate the **precipitation** of which being preferably controlled by seed crystals of riboflavin monohydrate.

SUMM It has been surprisingly found that seed crystals of riboflavin monohydrate are suitable for the **precipitation** of riboflavin dihydrate. When crystals of riboflavin monohydrate are brought into

contact with water, riboflavin dissolved in an supersaturated aqueous solution (fermentation broth) is immediately **precipitated** in the crystalline form of riboflavin dihydrate. The investigation of the nature of the crystalline forms revealed that in aqueous dispersions crystalline riboflavin monohydrate is rapidly transformed into crystalline riboflavin dihydrate.

SUMM A process for the preparation of crystalline riboflavin monohydrate is known from the prior art (cf. EP-A 995 749--**modification** B/C).

SUMM In step (a) of the process according to the invention a successful **precipitation** of the desired first crystalline form of riboflavin requires that the seed crystals be in the desired crystalline form, preferably riboflavin monohydrate, riboflavin dihydrate or riboflavin tetrahydrate, more preferably riboflavin monohydrate or riboflavin dihydrate. Furthermore, the seed crystals should be sterile not to contaminate the fermentation process by organisms from outside.

SUMM The seed crystals of riboflavin can be prepared in seed fermenters or in another suitable reactor. The riboflavin which is introduced as the starting material into the seed fermenters has to be fully diluted. Any impurity, i.e. any undissolved crystal of an undesired crystalline form, later in step (a) of the process will usually result in the **precipitation** of the identical undesired crystalline form thereby yielding an undesired intermediate (i.e. the first crystalline form of riboflavin). In particular, any impurity of riboflavin anhydrate I in the seed crystals inevitably results in the **precipitation** of riboflavin anhydrate I during the fermentation process and hence is to be avoided.

SUMM Spontaneous crystallization of the riboflavin anhydrate I does not occur. Preferably, the vaccination occurs at temperatures between 36° C. and 43° C. and at a riboflavin concentration of 0.16 g I.sup.-1 to 0.23 g I.sup.-1 in the fermentation broth. In step (b) of the process according to the invention the first crystalline form of riboflavin is isolated. This means that, when step (a) has been performed starting from the crude reaction slurry contained in a fermenter, preferably the major part of the biomass is removed from the reaction slurry. Preferably the first crystalline form of riboflavin is isolated by decantation, i.e. by separation of the overhead from the **precipitate** (biomass separation). Step (b) of the process according to the invention usually does not result in an isolation of pure riboflavin. In general, the isolated first crystalline form of riboflavin still contains impurities which have to be separated in further purification steps. The invention is particularly concerned with the removal of these impurities.

SUMM In a preferred embodiment of the process according to the invention the first crystalline form of riboflavin **precipitated** in step (a) and isolated in step (b) is pasteurized, preferably after step (b) but preferably prior to step (c). Preferably the pasteurization is performed by heating the first crystalline form of riboflavin which was separated from the major amount of biomass contained in the reaction slurry earlier in step (b). In a preferred embodiment the pasteurization is performed at a temperature ranging from 40° C. to 80° C., preferably from 60° C. to 75° C. Preferably the pasteurization is performed under acidic conditions. The pasteurization is preferably performed at a pH value of below 6, more preferably at a pH value of below 4. Preferred acids which may be added to an aqueous

suspension of the first crystalline form of riboflavin are **mineral acids**, preferably sulfuric acid or nitric acid, or organic acids, preferably carboxylic acids, most preferably formic acid or oxalic acid.

SUMM In a preferred embodiment of the process according to the invention the conditions in step (c) that decompose DNA are acidic conditions. Acidic conditions are preferably realized by the addition of an acid to the first crystalline form of riboflavin suspended in an aqueous slurry containing 0.5-50 wt.-%, preferably 2-10 wt.-% of riboflavin. In a preferred embodiment the **acid** is a **mineral acid** selected from the group consisting of sulfuric acid, nitric acid, phosphoric acid, hydrochloric acid, hydrobromic acid or an organic acid selected from the group consisting of acetic acid, formic acid and oxalic acid. The concentration of the acid in the aqueous slurry preferably should be higher than 10.sup.-4 mol I.sup.-1, preferably between 10.sup.-4 and 10.sup.-1 mol I.sup.-1, most preferably about 5 10.sup.-4 mol I.sup.-1. The pH value of the aqueous slurry should be preferably below 6, more preferably below 5 and most preferably below 4.

SUMM It has been surprisingly found that the decomposition of impurities of DNA, particularly of rDNA associated with crystals of riboflavin is strongly dependent on the nature of the crystalline form of riboflavin. While the decomposition of rDNA Is particularly difficult in case that riboflavin anhydrate I is **precipitated** during the fermentation, the decomposition of rDNA In the downstream is relatively fast if riboflavin dihydrate is formed during the fermentation. Without the intention of being bound to any theory, it is assumed that rDNA, released from harvested cells is strongly associated with the riboflavin crystals.

SUMM In a preferred embodiment of the process according to the invention the first crystalline form of riboflavin which is **precipitated** in step (a) is riboflavin dihydrate. In step (b) the **precipitated** crystalline riboflavin dihydrate is isolated, preferably by decantation of the majority of the biomass, and optionally pasteurized. It has now been observed that when suspending the isolated crystalline riboflavin dihydrate in water and heating the slurry to a temperature of above 70° C., the viscosity significantly increases. The high viscosity can be lowered upon stirring at a high speed for a few minutes.

SUMM In a preferred embodiment of the process according to the invention, step (c) Is performed at a temperature of between 60° C. and 75° C. using

(i) a **mineral acid**, preferably H.sub.2SO4, HNO.sub.3, HCl, HBr or H.sub.3PO.sub.4; or
(ii) a base, preferably NaOH, KOH or Ca(OH).sub.2; or
(iii) an organic acid, preferably formic acid, acetic acid, oxalic acid or citric acid.

SUMM In a preferred embodiment of the process according to the invention in step (c) an aqueous slurry containing the first crystalline form of riboflavin Is transferred into a reactor equipped with an impeller stirrer. Then, preferably a sufficient amount of **mineral acid** or organic acid is added. The temperature is increased, preferably by means of a jacket, preferably to a temperature of between 60° C. and 75° C., most preferably of about 70° C.
The stirring speed of the impeller stirrer is set to about 500 rpm. As soon as the viscosity raises, the stirring speed is increased,

preferably up to about 2000 rpm to again liquefy the slurry. After ca. 20 min of treatment the slurry is filtered. The crystals obtained can be characterized by XRD and the content of rDNA can be analyzed by PCR.

SUMM In a preferred embodiment of the process according to the invention the first crystalline form of riboflavin is a riboflavin hydrate, preferably riboflavin dihydrate, and the second crystalline form of riboflavin is riboflavin anhydrate I. The **precipitation** of the first crystalline form of riboflavin in step (a) is preferably controlled by addition of seed crystals, more preferably by seed crystals of a riboflavin hydrate, most preferably by seed crystals of riboflavin monohydrate or seed crystals of riboflavin dihydrate.

SUMM In a preferred embodiment of the process according to the invention riboflavin dihydrate is **precipitated** in step (a) (first crystalline form of riboflavin) which then in step (c) is transformed into riboflavin anhydrate I (second crystalline form of riboflavin). In the course of the transformation, rDNA and other compounds that are associated with the riboflavin crystals are released into the surrounding medium. In the solution the dissolved rDNA can be easily decomposed by any suitable condition or ingredient, e.g. by a **mineral acid** or an organic acid that decomposes dissolved DNA.

SUMM The invention relates to an efficient process for the purification and crystallization of riboflavin in which (recombinant) DNA is decomposed below the detection limit of conventional PCR. In a preferred embodiment the process comprises the formation and sterilization of suitable seed crystals, preferably seed crystals of riboflavin monohydrate or riboflavin dihydrate. In a preferred embodiment the **precipitation** of a first crystalline form of riboflavin, preferably riboflavin dihydrate, is initiated by means of said seed crystals in the fermenter. Furthermore, the process comprises the removal of DNA molecules associated with the first crystalline form of riboflavin by transforming the first crystalline form of riboflavin, preferably riboflavin dihydrate, into a second crystalline form of riboflavin, preferably riboflavin anhydrate I, under conditions that decompose diluted DNA. Preferably the transformation of the first crystalline form of riboflavin into the second crystalline form of riboflavin is performed by heating the suspended first crystalline form of riboflavin in the presence of an acid. The concentration of the acid is preferably above 10.sup.-4 mol I.sup.-1, the pH value of the solution is preferably below 6, more preferably below 5 and most preferably below 4.

DETD A sample of **modification B/C** (as described in EP-A 995 749; corresponding to riboflavin monohydrate) was investigated by combined DVS--gravimetry and combined DVS--x-ray diffraction, FIG. 3. The sample was fixed at ambient temperature and at 52% relative humidity (water vapor). In both combined methods, the relative humidity (RH) was constantly increased until a relative humidity of about 96% was reached. Then, the relative humidity was constantly decreased to 0%. Then, the humidity was increased up to 52% again to reach the starting point. The cycle was repeated a second time.

DETD The structure of riboflavin tetrahydrate is known as type C (**modification**). **Riboflavin** anhydrate III is a new crystalline form and is the third anhydrous modification besides riboflavin anhydrate I and riboflavin anhydrate II. Its X-ray diffractogram differs from all the other diffractograms of the crystalline forms of riboflavin.

DETD After sterilization and decantation of the major part of the biomass the remaining riboflavin slurry that contains 6 wt.-% of riboflavin crystals is treated by adding a **mineral acid**, preferably sulfuric acid, nitric acid, phosphoric acid and/or organic acid, preferably acetic acid, formic acid, oxalic acid. After adding the acid the concentration of the acid in the slurry was 5 10.sup.-4 mol I.sup.-1. The acidified slurry was stirred intensively.

DETD A process for the preparation of riboflavin tetrahydrate is described In U.S. Pat. No. 2,603,633. The process basically uses a solvent to rapidly **precipitate** the riboflavin in order to obtain the desired tetrahydrate "type C" (**modification**). The samples prepared by this method transform at a relative humidity of 95% in about 100 min into riboflavin dihydrate.

CLM What is claimed is:

1. Process for the purification of riboflavin comprising the steps of (a) **precipitating** a first crystalline form of riboflavin, (b) isolating the first crystalline form of riboflavin, (c) transforming the first crystalline form of riboflavin into a second crystalline form of riboflavin under conditions that decompose diluted DNA, and (d) isolating the second crystalline form of riboflavin, provided that at ambient temperature the first crystalline form of riboflavin is thermodynamically less stable than the second crystalline form of riboflavin.

8. Process according to claim 1, characterized in that in step (a) the **precipitation** of the first crystalline form of riboflavin is induced by means of seed crystals.

11. Process according to claim 1, characterized in that step (c) is performed at a temperature of between 60° C. and 75° C. using (i) a **mineral acid**, (ii) a base, or iii) an organic acid.

IT **83-88-5P**, Riboflavin, preparation
(process for the purification of riboflavin)

L109 ANSWER 33 OF 39 USPATFULL on STN

ACCESSION NUMBER:	2006:144595 USPATFULL Full-text
TITLE:	Mixtures of polypeptides, compositions containing and processes for preparing same, and uses thereof
INVENTOR(S):	Pinchasi, Irit, Ra'anana, ISRAEL Dolitzky, Ben-Zion, Petach-Tikva, ISRAEL Frenkel, Anton, Modiin, ISRAEL Schwartz, Michal, Rehovot, ISRAEL Arnon, Ruth, Rehovot, ISRAEL Aharoni, Rina, Rehovot, ISRAEL

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2006122113	A1	20060608
APPLICATION INFO.:	US 2005-223408	A1	20050909 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2004-608844P	20040909 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	COOPER & DUNHAM, LLP, 1185 AVENUE OF THE AMERICAS, NEW YORK, NY, 10036, US
NUMBER OF CLAIMS:	48

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 31 Drawing Page(s)
LINE COUNT: 3857
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides a composition comprising a mixture of polypeptides, wherein each polypeptide (a) is a copolymer of the amino acids L-glutamic acid, L-alanine, L-tyrosine, and L-lysine, and (b) may be in the form of a pharmaceutically acceptable salt; and wherein in the mixture (i) the polypeptides have an average molecular weight in the range 13,500 to 18,500 daltons, (ii) 13% to 38% of the polypeptides have a diethylamide group instead of a carboxyl group present at one end thereof, and (iii) 68% of the polypeptides have a molecular weight between 7,000 and 41,000 daltons. In an embodiment, the average molecular weight is 16,000 daltons, and processes for preparing and its uses.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD The invention includes salts of the polypeptide mixture of the invention. As used herein, the term "salts" refers to both salts of carboxyl groups and to acid addition salts of amino groups of the peptide molecule. Salts of a carboxyl group may be formed by means well known in the art and include inorganic salts, for example, sodium, calcium, ammonium, ferric or zinc salts, and the like, and salts with organic bases such as those formed for example, with amines, such as triethanolamine, arginine, or lysine, piperidine, procaine, and the like. Acid addition salts include, for example, salts with **mineral acids** such as, for example, hydrochloric acid or sulfuric acid, and salts with organic acids, such as, for example, acetic acid, citric acid or trifluoroacetic acid. Such salts are preferably used to modify the pharmaceutical properties of the peptide insofar as stability, solubility, etc., are concerned.

DETD Fourier Transformed Infra Red Spectrum (FTIR) Spectrum of the Polypeptide Mixture of the Invention (RS)

TABLE 4

IR absorption maxima of a 1% dispersion of the polypeptide mixture of the invention in KBr

Absorption (cm-.sup.1)	Assignment
1655.0	C.dbd.O stretching (amide I)
1550.6	N--H in-plane bending **modified** by C--N stretch
1406.0	CO2" symmetric vibration
1248.1	C--N stretching mode modified by N--H in-plane bending (amide III)

DETD Determination of molecular weights (MW) distribution in the polypeptide mixture of the invention by SEC-chromatography requires a suitable set of MW markers. As the polypeptide mixture of the invention differs from native protein, no commercial protein MW markers could be used for this purpose and markers related to the mixture of polypeptides of the invention ("polypeptide markers") had to be produced. In order to obtain marker set for MW calibration curve, five markers were designed with MW range from about 16,000 Da to 27,000 Da (table 6). The polypeptide markers were produced by recombinant methods. The markers cDNA were sub-cloned into pET-21a vector (Merck cat# 69740) and cloned into HMS174(DE3) E. coli strain (Merck cat# 69453). After expression, two **precipitations** and two chromatography steps gave the markers in at least 80% purity.

DETD Following copolymerization, process water is added and the protected polypeptides are subjected to **precipitation**, chopping, and dispersion for 1.25 hours. The protected polypeptides are then subjected to filtration and washing. The filter-cake is dried in a vacuum at 60° C.±5° C. at a pressure of less than 20 mmHg for 12 hours, and then subjected to milling. This yields a mixture of protected polypetides, wherein the side chain functional groups of two amino acids (glutamic acid and lysine) are protected to avoid cross-linking.

IT 50-02-2, Dexamethasone 50-18-0, Cyclophosphamide 50-23-7, Hydrocortisone 50-24-8, Prednisolone 50-44-2, 6-Mercaptopurine 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 50-53-3, biological studies 50-55-5, Reserpine 50-81-7, Vitamin C, biological studies 51-34-3, Scopolamine 51-43-4, Epinephrine 51-55-8, Atropine, biological studies 51-83-2, Carbachol 51-85-4, Cystamine 52-86-8, Haloperidol 53-03-2, Prednisone 54-85-3, Isoniazide 54-96-6, 3,4-Diaminopyridine 55-91-4, Isoflurophate 56-81-5, Glycerin, biological studies 56-94-0 57-00-1, Creatine 57-41-0, Phenytoin 58-38-8 58-73-1, Diphenhydramine 58-74-2, Papaverine 59-05-2, Methotrexate 59-30-3, Folic acid, biological studies 59-66-5, Acetazolamide 59-96-1, Phenoxybenzamine 67-20-9, Nitrofurantoin 68-88-2, Hydroxyzine 72-69-5, Nortriptyline 74-79-3, L-Arginine, biological studies 76-57-3, Codeine 79-43-6, biological studies 83-88-5, Riboflavin, biological studies 89-57-6, 5-Aminosalicylic acid 92-13-7, Pilocarpine 92-84-2, Phenothiazine 94-78-0, Phenazopyridine 98-92-0, Nicotinamide 99-20-7, Trehalose 100-97-0, Methenamine, biological studies 101-31-5, Hyoscyamine 113-53-1, Dothiepin 125-33-7, Primidone 130-95-0, Quinine 155-09-9, Tranylcypromine 298-46-4, Carbamazepine 298-50-0, Propantheline 302-79-4, Retinoic acid 303-98-0, Coenzyme Q10 438-60-8, Protriptyline 439-14-5, Diazepam 443-48-1, Metronidazole 446-86-6, Azathioprine 495-40-9D, Butyrophenone, derivs. 504-24-5, 4-Aminopyridine 523-87-5, Dimenhydrinate 541-15-1, Carnitine 569-65-3, Meclizine 578-68-7D, 4-Aminoquinoline, derivs. 599-79-1, Sulfasalazine 603-50-9, Bisacodyl 745-65-3, Alprostadil 768-94-5, Amantadine 846-50-4, Temazepam 915-30-0, Diphenoxylate 1134-47-0, Baclofen 1200-22-2, Lipoic acid 1309-42-8, Magnesium hydroxide 1406-16-2D, Vitamin D, derivs. 1406-18-4, Vitamin E 1622-61-3, Clonazepam 1668-19-5, Doxepin 2152-34-3, Pemoline 4205-90-7, Clonidine 4291-63-8, Cladribine 5633-20-5, Oxybutynin 6493-05-6, Pentoxifylline 7601-54-9, Sodium phosphate 7782-49-2, Selenium, biological studies 8063-16-9, Psyllium mucilloid 10041-19-7, Docusate 10118-90-8, Minocycline 11000-17-2, Vasopressin 11103-57-4, Vitamin A 14605-22-2, Tauroursodeoxycholic acid 14663-23-1, Dantrolene sodium 15722-48-2, Olsalazine 16679-58-6, Desmopressin 18378-89-7, Mithramycin 19794-93-5, Trazodone 19982-08-2, Memantine 22664-55-7, Metipranolol 23047-25-8, Lofepramine 26921-17-5, Timolol maleate 28981-97-7, Alprazolam 30562-34-6, Geldanamycin 32222-06-3, Calcitriol 34911-55-2, Bupropion 36505-84-7, Buspirone 41294-56-8, Alphacalcidol 47141-42-4, Levobunolol 51322-75-9, Tizanidine 51781-06-7, Carteolol 52365-63-6, Dipivefrin 53123-88-9, Rapamycin 53179-11-6, Loperamide 54910-89-3, Fluoxetine 57308-51-7, Carbidopa-levodopa mixture 59277-89-3, Acyclovir 59729-33-8, Citalopram 59803-98-4, Brimonidine 59865-13-3, Cyclosporine 60142-96-3, Gabapentin 61869-08-7, Paroxetine 63590-64-7, Terazosin 63659-18-7, Betaxolol 65271-80-9, Mitoxantrone 66711-21-5, Apraclonidine 68291-97-4, Zonisamide 68693-11-8, Modafinil 71320-77-9, Moclobemide 79617-96-2, Sertraline 79902-63-9, Simvastatin 80573-04-2, Balsalazide 82626-48-0, Zolpidem 83366-66-9, Nefazodone 84057-84-1, Lamotrigine 85650-52-8, Mirtazapine 85721-33-1, Ciprofloxacin 91524-16-2, Timolol hemihydrate 93413-69-5, Venlafaxine 97240-79-4,

Topiramate 107231-12-9, Botulinum toxin 107452-89-1, Ziconotide 119431-25-3, Eliprodil 120279-96-1, Dorzolamide 124937-51-5, Tolterodine 128298-28-2, Remacemide 130209-82-4, Latanoprost 136236-51-6, Rasagiline 138890-62-7, Brinzolamide 139755-83-2, Sildenafil 148553-50-8, Pregabalin 155206-00-1, Bimatoprost 157283-68-6, Travoprost 189261-10-7, Natalizumab 216503-57-0, Alemtuzumab 248281-84-7, Laquinimod
(therapeutic combinations containing mixts. of polypeptides comprising alanine, glutamic acid, lysine and tyrosine)

L109 ANSWER 34 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2004:321527 USPATFULL Full-text
TITLE: Enhanced propertied pharmaceuticals
INVENTOR(S): Mulvihill, Mark Joseph, East Northport, NY, UNITED STATES
Shaber, Steven Howard, Indianapolis, IN, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004254182	A1	20041216
APPLICATION INFO.:	US 2002-182076	A1	20021217 (10)
	WO 2001-US653		20010126

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-493865, filed on 28 Jan 2000, GRANTED, Pat. No. US 6376548

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-178878P	20000128 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WOODCOCK WASHBURN LLP, ONE LIBERTY PLACE, 46TH FLOOR, 1650 MARKET STREET, PHILADELPHIA, PA, 19103
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
LINE COUNT: 18780
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to compounds which are useful as enhanced propertied pharmaceutical compounds for both human and veterinary application. The pharmaceutical compounds which are suitable for use in this invention are those compounds which can be substituted with a moiety, said moiety comprising a substituent which enhances or changes the properties of the pharmaceutical compound. The chemical modification of drugs into labile derivatives with enhanced physicochemical properties that enable better transport through biological barriers is a useful approach for improving-drug delivery.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L109 ANSWER 35 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2004:267814 USPATFULL Full-text
TITLE: Systems and devices for photoelectrophoretic transport and hybridization of oligonucleotides
INVENTOR(S): Edman, Carl Frederick, San Diego, CA, UNITED STATES
Heller, Michael James, Encinitas, CA, UNITED STATES
Gurtner, Christian, La Jolla, CA, UNITED STATES
Formosa, Rachel, San Diego, CA, UNITED STATES
PATENT ASSIGNEE(S): Nanogen, Inc., San Diego, CA (U.S. corporation)

	NUMBER	KIND	DATE

PATENT INFORMATION:	US 2004209355	A1	20041021
APPLICATION INFO.:	US 2004-772744	A1	20040204 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2000-489855, filed on 24 Jan 2000, GRANTED, Pat. No. US 6706473 Continuation-in-part of Ser. No. US 1999-436311, filed on 8 Nov 1999, GRANTED, Pat. No. US 6569382 Continuation-in-part of Ser. No. US 1996-760933, filed on 6 Dec 1996, GRANTED, Pat. No. US 6652808		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	O'MELVENY & MEYERS, 114 PACIFICA, SUITE 100, IRVINE, CA, 92618		
NUMBER OF CLAIMS:	20		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	52 Drawing Page(s)		
LINE COUNT:	2398		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A platform for photoelectrophoretic transport and electronic hybridization of fluorescence labeled DNA oligonucleotides in a low conductivity electrolyte is described. A chemically stabilized semiconductor photodiode or photoconductor surface is coated with a streptavidin-agarose permeation layer. Micro-illumination of the surface generates photo-electrochemical currents that are used to electrophoretically transport and attach capture strands, preferably biotinylated DNA, to arbitrarily selected locations. The same process is then used to transport and electronically hybridize fluorescence labeled DNA target strands to the previously attached capture strands. Signal detection is accomplished either by a fluorescence scanner or a CCD camera. This represents a flexible electronic DNA assay platform that need not rely on pre-patterned microelectronic arrays.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DRWD [0092] FIGS. 48A and B. Tapping mode AFM images of a Mn.sub.2O.sub.3 film deposited onto single crystal n-type silicon. The film thickness of this sample is approximately 270 nm with a medium roughness of 50 nm. a) Low-resolution image showing the oriented **granular** structure of the Mn.sub.2O.sub.3 film. Arrows indicate larger **precipitates** on the surface. b) High-resolution surface plot of the same sample.

DETD [0215] FIG. 10 shows the write identity process is initiated by hybridizing a (B) identity psoralen **modified** DNA sequence that is also partially complementary to the (A) identity capture sequence existing in all four quadrants (locations). The psoralen molecules intercalate within the hybridized double-stranded DNA.

DETD [0249] The following procedure for deposition of Mn.sub.2O.sub.3 layers was modified from the original procedure published by Kainthla et al.: Individual samples of single crystal or amorphous silicon with dimensions of about 1 cm.sup.2 were cut from the respective wafers and sonicated in acetone followed by rinsing with isopropanol and water. (Alternatively, larger samples can be pre-scribed with a diamond scribe and broken into individual pieces after deposition of the Mn.sub.2O.sub.3 layer.) After drying, the samples were placed in plastic petri dishes and treated with buffered HF (2 min) to strip the native oxide layer. Immediately after thorough rinsing with deionized water the sample surfaces were sensitized by exposure (2 min) to an aqueous solution containing 1 wt % SnCl.sub.2 (Aldrich) and 4 vol % HCl. This step was followed by rinsing with 4 vol % HCl and deionized water. The sensitized surfaces were then decorated with Pd islands by immersion (2 min) in an aqueous solution containing 1 vol % HCl and 0.05 wt %

PdCl.sub.2 (Aldrich). Traces of Sn.sup.4+ were removed by soaking in 5% HCl for 5 min followed by rinsing with deionized water. The deposition of the Mn(OH).sub.2 layer was performed by adding a freshly prepared aqueous solution containing 0.25 M NH.sub.4Cl, 0.1 M NH.sub.4OH and 0.03 M MnCl.sub.2 to the samples in the petri dish. Upon addition of the solution the petri dishes were placed on a shaker table for 10 min to allow vigorous stirring. A light brownish **precipitate** was observed to form within 30-60 sec. After completion of the deposition reaction, the samples were rinsed thoroughly with deionized water and dried in air. At this point, the sample surfaces have a slightly structured, brown-grayish appearance. The thermal conversion of Mn(OH).sub.2 into Mn.sub.2O.sub.3 was accomplished by heating the samples on a heating block in high vacuum (10.sup.-5 to 10.sup.-6 torr) to 250 C for 15 min. The samples were left overnight to cool down to room temperature.

DETD [0259] A further modification involved the actual Mn(OH).sub.2 deposition step. It was observed that the use of 1.4 M NH.sub.4OH leads to immediate **precipitation** of Mn(OH).sub.2 and not to a gradual formation of a light brown **precipitate** as described in the original paper. This rapid **precipitation** was found to introduce further irreproducible behavior that we were able to avoid by decreasing the NH.sub.4OH concentration to 0.1 M. The resulting surfaces still displayed a certain degree of visual inhomogeneity but had very reproducible photoelectrochemical characteristics.

DETD [0260] FIGS. 48A and B show two tapping mode atomic force images of a typical Mn.sub.2O.sub.3 surface at 50 .quadrature.m and 5 .quadrature.m full scale, respectively. The surface has a **granular** structure with an average grain size of approximately 2 .quadrature.m and a mean roughness of 50 nm (with a small number of larger **precipitates**). The grains exhibit a preferred orientation probably caused by fluid flow during solution deposition of the Mn(OH).sub.2 precursor film. Film thickness' obtained from step height measurements ranged from 250 to 350 nm. This is at least a factor of ten more than the thickness reported by Kainthla et al. The difference reflects the increased deposition rate of Mn(OH).sub.2 that is caused by the lower concentration of NH.sub.4OH used in our procedure.

IT 83-88-5, Riboflavin, analysis 129-00-0, Pyrene, analysis 260-94-6, Acridine 82446-52-4, Lucifer Yellow
(as acceptor chromophore, in labeling polynucleotides for determination of nucleic acid by photonic energy transfer)

L109 ANSWER 36 OF 39 USPATFULL on STN

ACCESSION NUMBER: 2004:239292 USPATFULL Full-text

TITLE: Controlled release modifying complex and pharmaceutical compositions thereof

INVENTOR(S): Kannan, Muthaiyyan Esakki, Mumbai, INDIA
Krishnan, Anandi, Mumbai, INDIA
Sapre, Beena Amol, Mumbai, INDIA
Shah, Chitra Siddharth, Mumbai, INDIA
Patil, Atul Vishvanath, Mumbai, INDIA

PATENT ASSIGNEE(S): Glenmark Pharmaceuticals Ltd., Princeton, NJ, 08540 (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004185097	A1	20040923	
APPLICATION INFO.:	US 2004-762180	A1	20040121	(10)

	NUMBER	DATE

PRIORITY INFORMATION: IN 2003-1302003 20030131
US 2003-517589P 20031105 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LERNER, DAVID, LITTENBERG,, KRUMHOLZ & MENTLIK, 600 SOUTH AVENUE WEST, WESTFIELD, NJ, 07090
NUMBER OF CLAIMS: 145
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 2112
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed is a controlled release modifying complex for solid oral controlled release pharmaceutical compositions suitable for once-a-day administration. The composition comprises an active pharmaceutical ingredient, a release modifying complex and other required pharmaceutically acceptable excipients. The release modifying complex comprises a primary release modifying agent, a secondary release modifying agent and an auxiliary release modifying agent or varying combinations thereof, wherein said primary, secondary and auxiliary release modifying agents are present in amounts that synergistically effect and extend the release of active pharmaceutical ingredient.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0003] One of the most frequently utilized methods to extend the duration of drug action in the body and/or control blood level fluctuations is modification of the pharmaceutical dosage form. This is usually achieved with single or multi-component matrix systems such as **granules**, pellets, tablets or a combination of the above where the drug delivery is mainly controlled by a diffusion, osmotic or erosion mechanism.

SUMM [0027] In another aspect, the present invention relates to a controlled release pharmaceutical composition of an API comprising an API and a synergistic release modifying complex wherein said complex comprises, (a) a primary release **modifying** agent, (b) a secondary release **modifying** agent, and (c) an auxiliary release modifying agent, so that when ingested orally, said complex synergistically effects and extends release of the API.

SUMM [0028] In another aspect, the present invention relates to a controlled release pharmaceutical composition of an API comprising an API and a synergistic release modifying complex wherein said complex comprises, (a) a primary release **modifying** agent, or (b) a secondary release **modifying** agent, and (c) an auxiliary release modifying agent, so that when ingested orally, said complex synergistically effects and extends release of the API.

SUMM [0032] The present invention also relates to a process, for the preparation of a controlled release composition of an API suitable for once-a-day administration, comprising a wet **granulation**, dry **granulation**, slugging, roll compaction, direct compression or any other technique known in the pharmaceutical art.

DETD [0068] The other essential component of the release modifying complex is the auxiliary release modifying agent, selected from the starch derivatives. Examples of starch derivatives include pregelatinized starch, partially pregelatinized starch and retrograded starch. Pregelatinized starch is a starch that has been chemically and/or mechanically processed to rupture all or a part of the starch

granules and so as to render the starch flowable and directly compressible. Partially pregelatinized starch is a physically modified starch having the benefit of a soluble functionality and an insoluble functionality. Partial pregelatinization breaks the bond between the amylase and amylopectin, which are the two polymers, tightly bound in a specific spherocrystalline structure in starch. The partial pregelatinization process results in partial solubility, increased particle size, improved flow properties and compactability.

DETD [0069] Retrograded starch is a new pregelatinized starch, which is prepared by enzymatic degradation, **precipitation** (retrogradation) and washing with ethanol. The retrograded pregelatinized starch is a linear oligosaccharide and is characterized by a high specific surface area. The pharmaceutical composition of the present invention may contain either one of the above starch derivatives alone or a combination of the above starch derivatives as the auxiliary release modifying agents. All the above starch derivatives are contemplated to be used in the present invention. For example, the pharmaceutical composition contemplates the use of retrograded pregelatinized starch. The retrograded pregelatinized starch is commercially available as Prejel PA 5 PH from Avebe Inc. (The Netherlands).

DETD [0081] Another embodiment of the present invention provides methods of making a controlled release formulation of an active pharmaceutical ingredient by wet **granulation**, dry **granulation**, slugging, roll compaction, direct compression or any other technique known in the pharmaceutical art, wherein said formulation synergistically effects and extends the release of the API.

DETD [0082] The wet **granulation** process comprises the following steps. (1) Dry blending the mixture of API, primary release modifying agent, secondary release modifying agent, auxiliary release modifying agent and other required pharmaceutically acceptable additives to make a uniform homogenous blend. (2) Wet **granulating** the uniform blend. (3) Diminuting the wet mass. (4) Drying and sizing the **granules** to an optimum size suitable for compression. (5) Blending the sized **granules** with the required pharmaceutically acceptable additives/lubricants. (6) Compressing the blended **granules** into tablets.

DETD [0087] Nicotinic acid, which is a high soluble high dose API was mixed with high molecular weight polyethylene oxide (secondary release modifying agent), retrograded starch (auxiliary release modifying agent) and lactose monohydrate. The mixture was sifted through ASTM mesh no. 40, blended together in a blender to get a homogenous blend. The homogenous blend was **granulated** with water; the **granules** were dried in a fluid bed drier. The dried **granules** were reduced and sized to ASTM mesh no. 16 **granules** and then lubricated with talc and magnesium stearate.

TABLE 1-1

Sr. No.	Ingredient	Qty./ unit (mg)	% w/w of unit dosage form
1.	Nicotinic acid	500.00	66.66
2.	Polyethylene Oxide (Mol. Wt.: 4,000,000)	170.00	22.66
3.	Retrograded Starch	40.00	5.33
4.	Lactose Monohydrate	30.00	4.00
5.	Talc	5.00	0.66

6.	Magnesium Stearate	5.00	0.66
7.	Purified Water	q.s	q.s

DETD [0099] Clarithromycin, which is a low soluble high dose API, was mixed with a low molecular weight polyethylene oxide (primary release modifying agent) and/or high molecular weight polyethylene oxide (secondary release modifying agent), retrograded starch (auxiliary release modifying agent) and lactose monohydrate. The resulting mixture was sifted through ASTM mesh no. 40, blended together in a blender to get a homogenous blend. The homogenous blend was **granulated** with water; the **granules** were dried in a fluid bed drier. The dried **granules** were reduced and sized to ASTM mesh no. 16 **granules** and then lubricated with talc and magnesium stearate. The lubricated **granules** were compressed to tablets using the desired specific punches. The tablets were optionally coated with a polymer coating, using the polymers or coating agents not specifically designed for modification of drug release.

TABLE 6-1

Sr. No.	Ingredient	Qty./ unit (mg)	% w/w of unit dosage form
1.	Clarithromycin	500.00	50.00
2.	Polyethylene Oxide (Mol. Wt.: 200,000)	150.00	15.00
3.	Polyethylene Oxide (Mol. Wt.: 2,000,000)	50.00	5.00
4.	Retrograded Starch	150.00	15.00
5.	Lactose Monohydrate	120.00	12.00
6.	Talc	15.00	1.50
7.	Magnesium Stearate	15.00	1.50
8.	Purified Water	q.s	q.s

IT Drug delivery systems
(**granules**; controlled release pharmaceutical compns. containing polymers)

IT 50-04-4, Cortisone acetate 50-06-6, Phenobarbitone, biological studies 50-13-5, Pethidine hydrochloride 50-18-0, Cyclophosphamide 50-24-8, Prednisolone 50-33-9, Phenylbutazone, biological studies 50-34-0, Propantheline bromide 50-44-2, Mercaptopurine 50-54-4, Quinidine sulphate 50-59-9, Cefaloridine 50-63-5, Chloroquine phosphate 50-65-7, Niclosamide 50-81-7, Ascorbic acid, biological studies 50-98-6, Ephedrine hydrochloride 51-52-5, Propylthiouracil 52-01-7, Spironolactone 52-49-3, Benzhexol hydrochloride 52-67-5, Penicillamine 52-86-8, Haloperidol 53-03-2, Prednisone 53-86-1, Indomethacin 54-31-9, Frusemide 54-85-3, Isoniazid 55-03-8, Thyroxine sodium 55-63-0, Glyceryl trinitrate 56-53-1, Stilbestrol 56-75-7, Chloramphenicol 57-30-7, Phenobarbitone sodium 57-33-0, Pentobarbitone sodium 57-63-6, Ethinyloestradiol 57-68-1, Sulphadimidine 58-25-3, Chlordiazepoxide 58-33-3, Promethazine hydrochloride 58-54-8, Ethacrynic acid 58-56-0, Pyridoxine hydrochloride 58-71-9, Cefalothin Sodium 58-93-5, Hydrochlorthiazide 59-05-2, Methotrexate 59-30-3, Folic acid, biological studies 59-33-6, Mepyramine maleate 59-66-5, Acetazolamide 59-67-6, Niacin, biological studies 59-92-7, Levodopa, biological studies 61-24-5, Cephalosporin C 61-68-7, Mefenamic acid 61-72-3, Cloxacillin 63-45-6, Primaquine phosphate 64-75-5, Tetracycline hydrochloride 64-77-7, Tolbutamide 64-86-8, Colchicine 67-03-8, Thiamine hydrochloride 67-20-9, Nitrofurantoin 67-45-8, Furazolidone

67-92-5, Dicyclomine hydrochloride 68-22-4, Norethisterone 68-35-9, Sulphadiazine 68-41-7, Cycloserine 69-09-0, Chlorpromazine hydrochloride 69-44-3, Amodiaquine hydrochloride 69-52-3, Ampicillin Sodium 69-53-4, Ampicillin 71-63-6, Digitoxin 77-36-1, Chlorthalidone 77-67-8, Ethosuximide 79-41-4D, Methacrylic acid, polymers 80-08-0, Dapsone 83-12-5, Phenindione 83-43-2, Methylprednisolone 83-88-5, Riboflavine, biological studies 84-02-6, Prochlorperazine maleate 84-17-3, Dienoestrol 87-33-2, Isosorbide dinitrate 89-57-6, Mesalamine 97-77-8, Disulfiram 98-92-0, Nicotinamide 103-90-2, Paracetamol 113-52-0, Imipramine hydrochloride 114-07-8, Erythromycin 114-07-8D, Erythromycin, derivs. 114-49-8, Hyoscine hydrobromide 114-80-7, Neostigmine bromide 116-43-8, Succinylsulphathiazole 122-11-2, Sulphadimethoxine 124-94-7, Triamcinolone 126-07-8, Griseofulvin 127-48-0, Troxidone 127-69-5, Sulphafurazole 129-06-6, Warfarin sodium 129-20-4, Oxyphenbutazone 129-50-0, Ergometrine tartrate 129-51-1, Ergometrine maleate 130-26-7, Quiniodochlor 132-20-7, Pheniramine maleate 132-73-0, Chloroquine sulfate 141-01-5, Ferrous fumarate 142-88-1, Piperazine adipate 146-22-5, Nitrazepam 147-24-0, Diphenhydramine hydrochloride 148-79-8, Thiabendazole 148-82-3, Melphalan 149-64-4, Hyoscine butyl bromide 152-11-4, Verapamil hydrochloride 152-62-5, Dydrogesterone 152-72-7, Nicoumalone 298-46-4, Carbamazepine 299-29-6, Ferrous gluconate 299-95-6, Isoprenaline sulfate 309-43-3, Quinalbarbitone sodium 315-30-0, Allopurinol 317-34-0, Aminophylline 318-98-9, Propranolol hydrochloride 345-78-8, Pseudoephedrine hydrochloride 378-44-9, Betamethasone 389-08-2, Nalidixic Acid 396-01-0, Triamterene 404-82-0, Fenfluramine hydrochloride 439-14-5, Diazepam 440-17-5, Trifluoperazine hydrochloride 514-36-3, Fludrocortisone acetate 526-08-9, Sulphaphenazole 536-33-4, Ethionamide 549-18-8, Amitriptyline hydrochloride 549-56-4, Quinine bisulfate 550-70-9, Triprolidine hydrochloride 554-13-2, Lithium carbonate 569-59-5, Phenindamine tartrate 579-56-6, Isoxsuprine hydrochloride 595-33-5, Megestrol acetate 611-75-6, Bromhexine hydrochloride 614-39-1, Procainamide hydrochloride 630-93-3, Phenytoin sodium 637-32-1, Proguanil hydrochloride 642-78-4, Cloxacillin sodium 643-22-1, Erythromycin stearate 665-66-7, Amantadine hydrochloride 723-46-6, Sulphamethoxazole 738-70-5, Trimethoprim 751-94-0, Sodium fusidate 797-63-7, Levonorgestrel 804-63-7 834-28-6, Phenformin hydrochloride 859-18-7, Lincomycin hydrochloride 894-71-3, Nortriptyline hydrochloride 897-15-4, Dothiepin hydrochloride 965-90-2, Ethylestrenol 969-33-5, Cyproheptadine hydrochloride 1069-66-5, Sodium valproate 1094-08-2, Ethopropazine hydrochloride 1095-90-5, Methadone hydrochloride 1098-60-8, Triflupromazine hydrochloride 1104-22-9, Meclizine hydrochloride 1115-70-4, Metformin hydrochloride 1229-29-4, Doxepin hydrochloride 1229-35-2, Methdilazine hydrochloride 1319-82-0, Aminocaproic acid 1392-21-8, Kitasamycin 1406-05-9, Penicillin 1508-65-2, Oxybutynin hydrochloride 1642-54-2, Diethylcarbamazine citrate 2016-88-8, Amiloride hydrochloride 2030-63-9, Clofazimine 2058-46-0, Oxytetracycline hydrochloride 2753-45-9, Mebeverine hydrochloride 3116-76-5, Dicloxacillin 3485-14-1, Ciclacillin 3521-62-8, Erythromycin estolate 3577-01-3, Cefaloglycine 3736-81-0, Diloxanide furoate 3810-74-0, Streptomycin sulphate 3922-90-5, Oleandomycin 4205-91-8, Clonidine hydrochloride 4411-72-7 4697-36-3, Carbenicillin 5104-49-4, Flurbiprofen 6452-73-9, Oxprenolol hydrochloride 7232-21-5, Metoclopramide hydrochloride 7421-40-1, Carbenoxolone sodium 7447-40-7, Potassium chloride, biological studies 9002-89-5, Poly(vinyl alcohol) 9003-39-8, Polyvinylpyrrolidone 9004-34-6D, Cellulose, ethers 9004-57-3, Ethyl cellulose 9004-64-2, Hydroxypropyl cellulose 9004-65-3, Hydroxypropyl

methyl cellulose 9005-25-8, Starch, biological studies 9005-25-8D, Starch, derivs. 10206-21-0, Cefacetrile 10238-21-8, Glibenclamide 10592-13-9, Doxycycline hydrochloride 11111-12-9, Cephalosporin 13010-47-4, Lomustine 13292-46-1, Rifampicin 14538-56-8, Piperazine phosphate 14698-29-4, Oxolinic Acid 15307-79-6, Diclofenac sodium 15686-71-2, Cefalexin 15687-27-1, Ibuprofen 16051-77-7, Isosorbide-5-mononitrate 16595-80-5, Levamisole hydrochloride 16846-24-5, Josamycin 17575-22-3, Lanatoside C 17693-51-5, Promethazine theoclate 18609-21-7, Dextromethorphan hydrochloride 19237-84-4, Prazosin hydrochloride 19387-91-8, Tinidazole 20830-75-5, Digoxin 21535-47-7, Mianserin hydrochloride 21593-23-7, Cefapirin 21829-25-4, Nifedipine 22071-15-4, Ketoprofen 22232-54-8, Carbimazole 22260-51-1, Bromocryptine mesylate 23031-32-5, Terbutaline sulfate 25322-68-3, Polyethylene oxide 25953-19-9, Cefazolin 26787-78-0, Amoxicillin 26921-17-5, Timolol maleate 26973-24-0, Ceftezole 27025-49-6, Carfecillin 28657-80-9, Cinoxacin 28721-07-5, Oxcarbazepine 28981-97-7, Alprazolam 29122-68-7, Atenolol 31431-39-7, Mebendazole 31677-93-7, Bupropion hydrochloride 32780-64-6, Labetalol hydrochloride 33286-22-5, Diltiazem hydrochloride 34381-68-5, Acebutolol hydrochloride 34444-01-4, Cefamandole 35457-80-8, Midecamycin 35531-88-5, Carindacillin 35607-66-0, Cefoxitin 35834-26-5, Rosaramicin 36205-82-0 36322-90-4, Piroxicam 37091-66-0, Azlocillin
(controlled release pharmaceutical compns. containing polymers)

L109 ANSWER 37 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2004:83295 USPATFULL Full-text
TITLE: Combination therapy for the treatment of amyotrophic lateral sclerosis (ALS) with cyclooxygenase-2 (COX-2) inhibitor(s) and a second drug
INVENTOR(S): Isakson, Peter C., Morris Township, NJ, UNITED STATES
PATENT ASSIGNEE(S): Pharmacia Corporation, St. Louis, MO, 63167 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004063751	A1	20040401
APPLICATION INFO.:	US 2003-444071	A1	20030523 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-384104P	20020531 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BANNER & WITCOFF, 1001 G STREET N W, SUITE 1100, WASHINGTON, DC, 20001
NUMBER OF CLAIMS: 119
EXEMPLARY CLAIM: 1
LINE COUNT: 9874
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method of treating, preventing, or inhibiting ALS, in a subject in need of such treatment, inhibition or prevention. The method comprises administering to a subject one or more cyclooxygenase-2 selective inhibitor(s) or isomer(s) or pharmaceutically acceptable salt(s), ester(s), or prodrug(s) thereof, in combination with one or more second drugs, wherein the amount of the cyclooxygenase-2 selective inhibitor(s) or isomer(s) or pharmaceutically acceptable salt(s), ester(s), or prodrug(s) thereof in combination with the amount of second drug(s) constitutes an ALS treatment, inhibition or prevention effective amount.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L109 ANSWER 38 OF 39 USPATFULL on STN
ACCESSION NUMBER: 2000:157415 USPATFULL Full-text
TITLE: Purification and crystallization of riboflavin
INVENTOR(S): Wagner, Gerhard, Wehr, Germany, Federal Republic of
PATENT ASSIGNEE(S): Roche Vitamins Inc., Nutley, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6150364		20001121
APPLICATION INFO.:	US 1999-420824		19991019 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	EP 1998-119686	19981019

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Shah, Mukund J.
ASSISTANT EXAMINER: Sripada, Pavanaram K.
LEGAL REPRESENTATIVE: Waddell, Mark E., Haracz, Setphen M.Bryan Cave LLP
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
LINE COUNT: 524
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Purified and crystallized riboflavin is prepared by a process that includes dissolving needle-shaped riboflavin of the stable modification A form in an aqueous **mineral acid** solution at a temperature not exceeding about 30° C. with intensive intermixing. Active charcoal is then added to the resulting solution. After adsorption of the dissolved impurities from the solution onto the active charcoal, the solution containing the active charcoal is subjected to counter-current filtration over a ceramic membrane having a pore size of about 20 to about 200 nm. The resulting filtrate is treated with a five- to ten-fold amount of water (volume/volume) at a temperature not exceeding about 30° C. The resulting **precipitated**, spherical crystals of riboflavin are then separated by centrifugation or filtration. If desired, the spherical crystals of riboflavin may be washed with water and subsequently dried. The purified and crystallized riboflavin formed by this process is suitable for pharmaceutical and foodstuff applications.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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SUMM Various reports in the literature disclose different stable crystal modifications of riboflavin, which are formed by **precipitation**

from an alkaline solution. From such reports, however, no practical operating process has been developed, presumably due to the chemical degradation of riboflavin in alkaline solutions (see, for example, U.S. Pat. No. 2,603,633).

SUMM One embodiment of the invention is a process for the purification and crystallization of riboflavin that includes the steps of (a) dissolving needle-shaped riboflavin of a stable modification A form in an aqueous **mineral acid** solution at a temperature not exceeding about 30° C. with intermixing; (b) adding active charcoal to the solution to adsorb dissolved impurities from the solution onto the active charcoal; (c) filtering the solution containing the active charcoal by counter-current filtration over a ceramic membrane having a pore size of about 20 to about 200 nm to form a filtrate; (d) combining a five- to ten-fold amount of water (vol./vol.) at a temperature not exceeding about 30° C. with the filtrate in a crystallizer to form **precipitated** spherical crystals of riboflavin; and (e) separating the **precipitated** spherical crystals of riboflavin by centrifugation or filtration.

SUMM Yet a further embodiment is a process for supplementing a pharmaceutical or foodstuff with riboflavin that includes (a) obtaining purified riboflavin made by the following steps: (i) dissolving needle-shaped riboflavin of a stable modification A form in an aqueous **mineral acid** solution at a temperature not exceeding about 30° C. with intermixing; (ii) adding active charcoal to the solution to adsorb dissolved impurities from the solution onto the active charcoal; (iii) filtering the solution containing the active charcoal by counter-current filtration over a ceramic membrane having a pore size of about 20 to about 200 nm to form a filtrate; (iv) combining a five- to ten-fold amount of water (vol./vol.) at a temperature not exceeding about 30° C. with the filtrate in a crystallizer to form **precipitated** spherical crystals of riboflavin; and (v) separating the **precipitated** spherical crystals of riboflavin by centrifugation or filtration. The riboflavin from step (v) is then combined with a pharmaceutical composition or with a foodstuff.

SUMM This process includes dissolving needle-shaped riboflavin of the stable modification A form in an aqueous **mineral acid** solution at a temperature not exceeding about 30° C. with intensive intermixing. Active charcoal is then added to the resulting solution. After adsorption of the dissolved impurities in the solution onto the active charcoal, the solution is subjected to counter-current filtration over a ceramic membrane having a pore size of about 20 to about 200 nm to separate the charcoal from the solution. The resulting filtrate is treated with a five- to ten-fold amount (vol./vol.) of water (relative to the volume of the solution) at a temperature not exceeding about 30° C. which forms a **precipitate** of spherical riboflavin crystals. The **precipitated**, spherical crystals of riboflavin are then separated by centrifugation or filtration.

SUMM In the first stage of the process of the present invention, the riboflavin starting material, in dry or filter-moist form, is dissolved in an aqueous **mineral acid** solution. The dissolution of the starting material takes place by a protonation reaction. In the dissolution procedure, fermentation residues, such as proteins, peptides, and amino acids, and/or chemical byproducts, become liberated and are present in the solution partly dissolved and partly in solid form.

SUMM The **mineral acid** used in the present process may be, for example, hydrochloric acid or nitric acid. Hydrochloric acid is preferred. The concentration of the **mineral acid** is about 10% to about 65% (wt.).

SUMM Generally, in the dissolution step, the amount of riboflavin relative to the amount of aqueous **mineral acid** depends on the nature of the **mineral acid**, the concentration of the solution, and the dissolution temperature.

SUMM The dissolution of the needle-shaped riboflavin in the aqueous **mineral acid** solution is carried out at temperatures up to a maximum of 30° C., preferably at about 5 to about 25° C., such as for example, at about 10 to about 20° C. The solution is preferably subjected to intensive intermixing, for example by intensive stirring. The intensity of such "intensive intermixing" or stirring may be expressed in terms of the energy input/volume. In the present case said energy input/volume of the intensive intermixing is suitably in the range from about 1 to about 3 kW/m.sup.2, preferably about 2.3 to about 2.5 kW/m.sup.2.

SUMM In the next stage of the process, active charcoal is added to the riboflavin/aqueous **mineral acid** solution. The impurities present in dissolved form are then adsorbed onto the active charcoal.

SUMM The active charcoal may be powdered or **granulated.** In the present process, about 0.5 to about 9% (wt.), preferably about 3% (wt.) (based on the riboflavin content) of the active charcoal is added to the riboflavin/**mineral acid** solution for the adsorptive removal of the dissolved impurities. Depending on the impurities, the active charcoal may be left in the solution for up to about 12 hours, preferably from about 0.5 to about 3 hours.

SUMM If desired, in addition to active charcoal, a filter aid may be added to the riboflavin/**mineral acid** solution. For example, about 2 to about 9% (wt.) (based on the riboflavin content) of a filter aid may be used. Under the term "filter aid" there is generally understood an agent, which, in the case of a suspension with relatively little solid component, enables a filter cake to form which is more easily separated from the surface of the filter upon which it has formed, or, in the case of a filtered medium containing a dense, solid component of a slimy nature, renders the collected filter cake looser in consistency and thus more easily separable than otherwise. The filter aid is, as already mentioned, either added to the riboflavin/ **mineral acid** solution with active charcoal for filtration, or, alternatively, coated onto the filter prior to its use in the filtration. Commonly employed filter aids include cellulose, silica gel, kieselguhr, perlite and sawdust, and function in a physical/mechanical way, i.e. do not exert any chemical effect on the medium being filtered; they are essentially insoluble in said medium. For the purposes of the present process the bulk density of the filter aid is suitably in the range from about 110 to about 300 g/l, and its mean particle size is suitably in the range from about 5 to about 160 microns. Suitable filter aids in the present case include, for example, ARBOCEL® BWW 40 and B 800 from Rettenmaier & Sohne GmbH +Co.

SUMM The separation of the active charcoal, the optional filter aid, and any undissolved fermentation residue from the riboflavin/**mineral acid** solution is carried out by subsequent counter-current

filtration. Counter-current filtration is carried out over a ceramic membrane that has a pore size of about 20 to about 200 nm, preferably about 50 nm.

SUMM After counter-current filtration, the riboflavin/**mineral acid** solution is caused to **precipitate** (i.e., crystallize), which is effected by the addition of a five- to ten-fold amount of water (relative to the volume of the riboflavin/**mineral acid** solution). The resulting deprotonization of the riboflavin present in the aqueous solution leads to its **precipitation.**

SUMM The temperature of the solution in which the crystallization takes place may be varied from about 0 to 30° C., depending on the production method and the degree of impurity of the riboflavin. Especially in the case of synthetically produced riboflavin, the temperature may be increased to 30° C. In the case of fermentative or relatively clean riboflavin, temperatures below 10° C. are generally sufficient to cause **precipitation.** Preferably, however, a **precipitation** temperature of about 4 to 10° C. is selected.

SUMM The crystallization of riboflavin may be carried out batchwise or continuously, preferably continuously. Cascades or individual vessels may be used as the crystallizer apparatus. Especially in the case of individual vessels, it is preferable to introduce the riboflavin solution at different positions in the vessel. Within the crystallizer, a very good macroscopic intermixing must be set up in every case. This may be accomplished, for example, using a two-stage stirring device, with the feed solutions displaced by 180° that are fed on to upper and lower stirrer levels. To accomplish the crystallization, water is preferably introduced at the upper level and the riboflavin/**mineral acid** solution is introduced at the lower level.

SUMM Rather, growth of needle-shaped crystals in the present process is from an initially crystallized-out, small, probably amorphous, crystal seed. The dendritic crystals obtained in this process correspond to the more soluble **modification B** or **C** forms of **riboflavin**, and have adequate storage stability. Furthermore, because of the more unstable modification and larger surface area of these crystals, they have superior dissolution properties and, by virtue of their spherical shape, outstanding flow properties. Moreover, the process in accordance with the invention affords riboflavin crystals with a higher abrasion resistance than in the case of agglomerates.

DETD The solution of riboflavin in hydrochloric acid was then crystallized in a continuously operating **precipitation** crystallizer. The 3 l **precipitation** crystallizer was first filled with about 2 l of water and the liquid was stirred at 100 rpm with a two-stage inclined flat blade paddle stirrer, and subsequently cooled to 10° C. Thereafter, at about 10° C. 1590 g/h of the solution of riboflavin in hydrochloric acid was continuously added to the crystallizer at the upper stirrer position. Simultaneously and continuously about 9000 g/h of water was added to the crystallizer at the lower stirrer position.

DETD About 2-4 minutes after the riboflavin/hydrochloric acid solution had been added to the **precipitation** crystallizer, the riboflavin began to crystallize out of solution as orange-yellow crystals. Initially, the separated crystals appeared to be flocculent. After 20-30

minutes, the crystals changed into **granular** particles. The crystal suspension was then drained off continuously until the 3 l mark (double jacket end) had been reached in the crystallizer (i.e., after about 7 minutes). The valve was then adjusted so that the level remained approximately at the 3 l mark. The discharged suspension was added directly to a P3 suction filter where the solid was separated from the solution.

DETD In this example, the starting material was chemically produced and had a riboflavin content of 98%. The starting material was dissolved as described in Example 1. The counter-current filtration was carried out as described in Example 2. The crystallization was carried out at 20° C. by adding 1030 g/h of a riboflavin/hydrochloric acid solution and 15060 g/h of water to a **precipitation** crystallizer. Filtration and washing were carried out as described in Example 1. The crystallizate was dried as described in Example 2.

CLM What is claimed is:

1. A process for the purification and crystallization of riboflavin comprising the steps of: (a) dissolving needle-shaped riboflavin of a stable modification A form in an aqueous **mineral acid** solution at a temperature not exceeding about 30° C. with intermixing; (b) adding active charcoal to the solution to adsorb dissolved impurities from the solution onto the active charcoal; (c) filtering the solution containing the active charcoal by counter-current filtration over a ceramic membrane having a pore size of about 20 to about 200 nm to form a filtrate; (d) combining a five- to ten-fold amount of water (vol./vol.) at a temperature not exceeding about 30° C. with the filtrate in a crystallizer to form **precipitated** spherical crystals of riboflavin; and (e) separating the **precipitated** spherical crystals of riboflavin by centrifugation or filtration.

2. A process according to claim 1 wherein the **mineral acid** is hydrochloric acid or nitric acid.

3. A process according to claim 2 wherein the **mineral acid** is hydrochloric acid.

15. A process according to claim 1 further comprising the steps of collecting, separating, and drying the **precipitated**, spherical crystals of riboflavin on a band filter.

16. A process according to claim 1 further comprising intensively intermixing the riboflavin and **mineral acid** solution in step (a).

20. A process for supplementing a pharmaceutical or foodstuff with riboflavin comprising: (a) obtaining purified riboflavin made by the following steps: (i) dissolving needle-shaped riboflavin of a stable modification A form in an aqueous **mineral acid** solution at a temperature not exceeding about 30° C. with intermixing; (ii) adding active charcoal to the solution to adsorb dissolved impurities from the solution onto the active charcoal; (iii) filtering the solution containing the active charcoal by counter-current filtration over a ceramic membrane having a pore size of about 20 to about 200 nm to form a filtrate; (iv) combining a five- to ten-fold amount of water (vol./vol.) at a temperature not exceeding about 30° C. with the filtrate in a crystallizer to form **precipitated** spherical crystals of riboflavin; and (v) separating the **precipitated** spherical crystals of riboflavin by centrifugation or filtration; and (b) combining the riboflavin from

step (v) with a pharmaceutical composition or foodstuff.

IT **83-88-5P**, Riboflavin, preparation
(process for purification and crystallization of riboflavin)

L109 ANSWER 39 OF 39 USPATFULL on STN

ACCESSION NUMBER:	71:42557 USPATFULL Full-text		
TITLE:	EXTRACTION OF STEROIDAL MATERIALS FROM VEGETABLE MATERIALS		
INVENTOR(S):	Hardman, Roland, Bradford-on-Avon, England		
PATENT ASSIGNEE(S):	National Research Development Corporation, London, England		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 3620919		19711116
APPLICATION INFO.:	US 1968-751760		19680812 (4)
	NUMBER		DATE
PRIORITY INFORMATION:	GB 1967-39765		19670830
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Monacell, A. Louis		
ASSISTANT EXAMINER:	Nath, Gary M.		
LEGAL REPRESENTATIVE:	Jacobs & Jacobs		
NUMBER OF CLAIMS:	23		
LINE COUNT:	688		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The yield of recoverable steroidal saponins and sapogenins from steroidal sapogenin affording vegetable materials is increased by treating the vegetable material with a regulator prior to recovery of the steroidal material. The regulator is a substance capable of modifying normal plant metabolism or normal plant growth characteristics and the chemically diverse regulators are selected from naturally occurring and synthetic plant growth regulators including auxins, hormones and herbicides, sulphydryl inhibitors, regulators of steroid metabolism or lipid metabolism, naturally occurring and racemic α-amino acids, vitamins of the B group, rutin and water-soluble derivatives of vitamin A and tocopherol, growth factor analogues including vitamin and amino acid antimetabolites and penicillin, griseofulvin and chloramphenicol antibiotics. Diosgenin is recovered from species of Dioscorea, Trigonella and Balanites by incubating the vegetable material with regulator in an aqueous medium for up to 72 hours, hydrolyzing the incubated product with hydrochloric acid and solvent extracting sapogenins from the hydrolysate. Yields are further increased by also adding steroid precursors or C.sub.10 to C.sub.36 saturated hydrocarbons during incubation.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD The recovery of sapogenins from the treated product may conveniently be carried out by treating the product with a **mineral acid** to hydrolyse the glycosidic linkages, for example an incubation product may be heated, e.g., up to reflux temperature, with 2N hydrochloric acid for up to about 5 hours when the sapogenins, which are acid-insoluble, are released. Other nonoxidizing **mineral acids** such as sulfuric acid may also be used in this hydrolysis step as may other acid materials such as acid salts. The acid-insoluble material may then be separated from the hydrolysate, e.g., by filtration or centrifugation, and the sapogenins recovered by extracting the acid-free acid-insoluble residue with a sapogenin solvent such as

petroleum ether.

DETD Procedure C is modified as Procedure D/a in which the incubation is carried out without regulator, the regulator being added after the hydrochloric acid but before the acid hydrolysis, and as Procedure D/b in which the incubation is carried out without regulator, the regulator being added before the hydrochloric acid and acid hydrolysis. In experiments 1-16 2.5 g. portions of the dried powdered D. deltoidea tubers are added to a flask containing IAA when used (IAA is introduced as an ethanolic solution and the solvent then removed), 25 mls. tap water added, the mixture shaken for 5 minutes, a further 25 mls. tap water washed down the inside of the flask which is then set aside for incubation in the dark at 37° C. The product is then hydrolysed and the acid insoluble material extracted as described in procedure A to give a crude diosgenin. This product is assayed by a densiometric thin layer chromatographic procedure using a Chromoscan recording and integrating densitometer. The results obtained are shown in table II below.

TABLE II

DETD Regulator	Concentration p.p.m.	Incubation Time Hours	% Increase D.	F.	B.
Pharmamedia	10.sup. 5	6	28		
Proflo	10.sup. 5	48	5		
Yeatex granules	10.sup. 5	6	39		
Yeatex super	10.sup. 5	48	8		
Lipostabil	5+ 10.sup. 4	24	48		
Vosolastine	2+ 10.sup. 5	24	42		

DETD Regulator:	Concentration p.p.m.	Incubation Time hours	% Increase D.	F.	B.
ethyl-α-(4-chloro-phenoxy)-α -methyl-propionate	10.sup.5	48	6		
ethyl-α-(4-chloro-phenoxy)-α -methyl-propionate	5+10.sup.4	24	34		
ethyl-α-(4-chloro-phenoxy)-α-methyl-propionate	5+10.sup.4	24	8		
Alloxan monohydrate	400	24	6		
Alloxan monohydrate	400	24		8	
N-6-benzyl adenine	400	48		6	
2,4-dichlorophenoxy acetic acid	400	24		10	
2,4,5-trichlorophenoxy acetic acid	400	24	9		
2,4,5-trichlorophenoxy propionic acid	10.8	12		15	
3-indole-butyric acid	400	6	8		
iodo acetic acid	400	72	16		
iodo acetic acid	400	24		8	
iodoacetamide	400	48	10		
iodosobenzoic acid	400	6	13		
α-naphthalene acetic acid	400	72	5		
α-naphthalene acetic acid	400	6	9		
α-naphthalene acetic acid					

	400	24		6
N-ethyl maleimide	400	72	5	
Maleic acid hydrazide	400	24	6	
Maleic acid hydrazide	400	6	7	
β-(2-furyl) acrylic acid				
	400	24	6	7
β-(2-furyl) acrylic acid				
	400	6	8	
1,1'-dimethyl-4,4' -dipyridylium Weedol (ICI) granules				
	1.6+10.sup.3	24	8	
Nicotinic acid amide	400	24	12	
Pyridoxine hydrochloride				
	400	24	5	
Riboflavin	400	6	13	
Thiamine hydrochloride	400	24	11	
D-Calcium pantothenate	400	24	6	
Choline chloride	400	24	8	
Acetylcholine chloride	400	24	15	
Folic acid	400	24	7	
Meso inositol	400	24	15	
Nicotinic acid	400	24	7	
Pyridoxal hydrochloride				
	400	24	15	
P-amino benzoic acid	400	24	11	
DL-α-tocopherol acetate				
	6+10.sup.3	6	14	
Rutin (rutoside)	400	6	12	
Vitamin A, Acetate	400	6	8	
DL-ethionine	400	24	13	
DL-3-thienyl DL-Alanine				
	400	24	6	
Glycine	400	6	14	
Allyl-DL-glycine	400	6	19	
DL-β-phenyl-lactic acid				
	400	6	9	
α-picolinic acid hydrochloride				
	400	24	14	
2-chloro-4-aminobenzoic acid				
	400	24	8	
Oxythiamine hydrochloride				
	400	24	15	
DL-desthiobiotin	400	24	14	
Desoxypyridoxine hydrochloride				
	400	6	11	
Chloramphenicol	2+10.sup.4	24	13	
Propranol hydrochloride				
	2+10.sup.3	24	17	
Herbisan-5[(diethyl dithio bis(thionoformate), 58%]				
	4+10.sup.3	24	6	
5-bromo-6-methyl-3-(1-methylpropyl)uracil				
	400	24	6	
Griseofulvin	5+10.sup.4	48	5	
Penicillin G, sodium salt				
	5+10.sup.4 units per g. of air dried tuber.	48	5	
Orotic acid (uracil 4-carboxylic acid)				
	400	48	14	

3-amino-1,2,4-triazole 400 48 9
DL-isoleucine 4+10.sup.3 48 7
IT 50-71-5 54-22-8 56-40-6, biological studies 56-75-7 58-56-0
59-67-6, biological studies 60-31-1 61-82-5 64-69-7 65-22-5
65-86-1 67-03-8 67-21-0 67-48-1 69-57-8 77-06-5 **83-88-5**
, biological studies 86-87-3 87-51-4, biological studies 87-89-8
93-72-1 93-76-5 94-75-7, biological studies 98-92-0 123-33-1
125-67-7 126-07-8 127-47-9 128-53-0 133-32-4 137-08-6
144-48-9 148-51-6 150-13-0 153-18-4 314-40-9 318-98-9
443-79-8 502-55-6 539-47-9 614-05-1 636-20-4 636-80-6
637-07-0 828-01-3 1214-39-7 2457-76-3 3685-48-1 4685-14-7
7685-44-1 11096-62-1 12751-36-9 12751-39-2 12753-66-1
12753-68-3 27323-35-9
(plant regulator, steroidal sapogenins and saponins of medicinal plants in response to)

FILE 'HOME' ENTERED AT 10:35:27 ON 29 MAR 2007

SEARCH HISTORY

=> d his nofile

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     (FILE 'HOME' ENTERED AT 09:29:42 ON 29 MAR 2007)

     FILE 'STNGUIDE' ENTERED AT 09:30:29 ON 29 MAR 2007

     FILE 'CAPLUS' ENTERED AT 09:31:37 ON 29 MAR 2007
               E US2005-552137/APPS
L1           1 SEA ABB=ON  US2005-552137/AP
               D SCAN

     FILE 'REGISTRY' ENTERED AT 09:32:10 ON 29 MAR 2007
               E RIBOFLAVIN/CN
               E RIBOFLAVIN B/CN
               E RIBOFLAVIN C/CN
               E RIBOFLAVIN A/CN
L2           1 SEA ABB=ON  RIBOFLAVIN/CN

     FILE 'REGISTRY' ENTERED AT 09:33:42 ON 29 MAR 2007
               D IDE

     FILE 'CAPLUS' ENTERED AT 09:35:14 ON 29 MAR 2007
L3         191 SEA ABB=ON  FRANKE D?/AU
L4         583 SEA ABB=ON  HILL F?/AU
L5        4551 SEA ABB=ON  MARTIN C?/AU
L6           4 SEA ABB=ON  KNEBEL T?/AU
L7           1 SEA ABB=ON  L6 AND (L3 OR L4 OR L5)
L8       19773 SEA ABB=ON  L2
L9          14 SEA ABB=ON  (L3 OR L4 OR L5 OR L6) AND L8
               D SCAN TI
               D SCAN L1
L10     131793 SEA ABB=ON  GRANUL?/OBI
L11          3 SEA ABB=ON  (L3 OR L4 OR L5 OR L6) AND L8 AND L10
L12      26078 SEA ABB=ON  GRANUL?/CW
L13      47732 SEA ABB=ON  FLUIDIZED BED#/OBI
L14          5 SEA ABB=ON  L8 AND L12 AND L13
L15      26851 SEA ABB=ON  ACID#/OBI(L)(MINERAL/OBI OR INORG?/OBI)
L16     123048 SEA ABB=ON  PRECIPITAT?/OBI
L17    1029830 SEA ABB=ON  MODIF?/BI
L18       5394 SEA ABB=ON  B/BI(2A)L17
L19       9231 SEA ABB=ON  C/BI(2A)L17
L20         51 SEA ABB=ON  BC/BI(2A)L17
L21         19 SEA ABB=ON  L8 AND (L18 OR L19 OR L20)
               D SCAN L1
L22       1555 SEA ABB=ON  L8(L)PREP/RL
L23          3 SEA ABB=ON  L22 AND (L18 OR L19 OR L20)
L24          3 SEA ABB=ON  L21 AND (L10 OR L13 OR L15 OR L16)
L25          3 SEA ABB=ON  L8 AND L12 AND L15
L26          3 SEA ABB=ON  L8 AND L15 AND L16
               D SCAN TI

     FILE 'WPIX' ENTERED AT 09:43:02 ON 29 MAR 2007
L27         79 SEA ABB=ON  FRANKE D?/AU
L28        156 SEA ABB=ON  HILL F?/AU
L29        787 SEA ABB=ON  MARTIN C?/AU
L30          5 SEA ABB=ON  KNEBEL T?/AU
L31       3154 SEA ABB=ON  RIBOFLAVIN#/BI,ABEX OR RIBO FLAVIN#/BI,ABEX OR
               VITAMIN B2/BI,ABEX
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L32      153807 SEA ABB=ON  GRANUL?/BI,ABEX
L33        6414 SEA ABB=ON  FLUIDIZED BED#/BI,ABEX
L34      139368 SEA ABB=ON  PRECIPITAT?/BI,ABEX
L35       32098 SEA ABB=ON  ACID#/BI;ABEX(2A)(MINERAL/BI,ABEX OR INORG?/BI,ABEX
                )
L36      323133 SEA ABB=ON  MODIF?/BI,ABEX
L37        5865 SEA ABB=ON  L36(2A)B/BI,ABEX
L38        4314 SEA ABB=ON  L36(2A)C/BI,ABEX
L39           5 SEA ABB=ON  L36(2A)BC/BI,ABEX
                E RIBOFLAVIN/CN
L40           2 SEA ABB=ON  (RIBOFLAVIN/CN OR "RIBOFLAVIN HYDROCHLORIDE"/CN)
L41        1923 SEA ABB=ON  L40/DCR
                SEL SDRN,SDCN,DCSE L40
L42        1924 SEA ABB=ON  (0503/DRN,DCN,DCRE OR R00503/DRN,DCN,DCRE OR
                R16015/DRN,DCN,DCRE OR R18174/DRN,DCN,DCRE OR 105627-0-0-0/DRN,
                DCN,DCRE OR 105627-0-1-0/DRN,DCN,DCRE)
L43           4 SEA ABB=ON  (L27 OR L28 OR L29 OR L30) AND (L31 OR L41 OR L42)
                AND (L32 OR L33 OR L34 OR L35 OR L36)
                D TRIAL 1-4
L44       15081 SEA ABB=ON  FLUIDISED BED#/BI,ABEX

     FILE 'STNGUIDE' ENTERED AT 09:48:24 ON 29 MAR 2007

     FILE 'WPIX' ENTERED AT 09:51:25 ON 29 MAR 2007
                E B03-C+ALL/MC
                E B12-M11B+ALL/MC
                E  B12-M11D+ALL/MC
                E D03-H01T+ALL/MC
                E B12-J01+ALL/MC
                E D05-C10+ALL/MC
                E D05-H13+ALL/MC
                E E06-D17+ALL/MC
                E E11-Q01+ALL/MC
                E B12-J01+ALL/MC
                E D03-G01+ALL/MC
                E D03-H01E+ALL/MC
                E B12-L09+ALL/MC

     FILE 'STNGUIDE' ENTERED AT 09:51:48 ON 29 MAR 2007

     FILE 'WPIX' ENTERED AT 09:53:46 ON 29 MAR 2007
L45        1511 SEA ABB=ON  B03-C/MC OR C03-C/MC
L46        7193 SEA ABB=ON  B12-M11D/MC OR C12-M11D/MC
L47           8 SEA ABB=ON  (L31 OR L41 OR L42 OR L45) AND (L37 OR L38 OR L39)

L48          15 SEA ABB=ON  (L31 OR L41 OR L42 OR L45) AND (L32 OR L46) AND
                (L33 OR L44)
L49           2 SEA ABB=ON  (L31 OR L41 OR L42 OR L45) AND (L32 OR L46) AND
                (L33 OR L44) AND (L34 OR L35)
L50           4 SEA ABB=ON  (L31 OR L41 OR L42 OR L45) AND (L32 OR L46) AND
                (L33 OR L44) AND (L34 OR L35 OR L36)
L51          16 SEA ABB=ON  (L31 OR L41 OR L42 OR L45) AND L34 AND L35
L52           3 SEA ABB=ON  (L31 OR L41 OR L42 OR L45) AND L34 AND L35 AND
                (L32 OR L46)
L53           5 SEA ABB=ON  (L31 OR L41 OR L42 OR L45) AND L34 AND L35 AND
                (L32 OR L46 OR L36)
L54           2 SEA ABB=ON  L53 NOT L52
                D KWIC 1-2

     FILE 'WPIX' ENTERED AT 09:58:20 ON 29 MAR 2007
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L55             6 SEA ABB=ON  L31(3A)L36
L56             4 SEA ABB=ON  L55 NOT (L47 OR L43)
                  D KWIC 1-4
                  D QUE L49
                  D QUE L52
L57             2 SEA ABB=ON  (L31 OR L41 OR L42 OR L45) AND L34 AND L35 AND
                  (L33 OR L44)

     FILE 'USPATFULL' ENTERED AT 10:00:47 ON 29 MAR 2007
L58          1373 SEA ABB=ON  L2
L59         42967 SEA ABB=ON  MODIF?(2A)(B OR C OR BC)
L*** DEL        0 S MODIF?(2A)(B OR C OR BC)/IT
L60           306 SEA ABB=ON  (MODIF?(2A)(B OR C OR BC))/IT
L61            43 SEA ABB=ON  L58 AND (L59 OR L60)
L62            41 SEA ABB=ON  FRANKE D?/AU
L63           156 SEA ABB=ON  HILL F?/AU
L64           650 SEA ABB=ON  MARTIN C?/AU
L65             1 SEA ABB=ON  KNEBEL T?/AU
L66          9695 SEA ABB=ON  RIBOFLAVIN# OR RIBO FLAVIN# OR VITAMIN B2
L67          1387 SEA ABB=ON  (RIBOFLAVIN# OR RIBO FLAVIN# OR VITAMIN B2)/IT
L68             1 SEA ABB=ON  (L62 OR L63 OR L64 OR L65) AND (L58 OR L66 OR L67)
                  AND (L59 OR L60)
L69        274514 SEA ABB=ON  GRANUL?
L70          9334 SEA ABB=ON  GRANUL?/IT
L71             4 SEA ABB=ON  (L62 OR L63 OR L64 OR L65) AND (L58 OR L66 OR L67)
                  AND (L59 OR L60 OR L69 OR L70)
L72             2 SEA ABB=ON  L67(L)L60
L73             6 SEA ABB=ON  L66(2A)L59
L74         39711 SEA ABB=ON  FLUIDI? BED#
L75          3126 SEA ABB=ON  (FLUIDI? BED#)/IT
L76        396897 SEA ABB=ON  PRECIPITAT?
L77          1758 SEA ABB=ON  PRECIPITAT?/IT
L78          3140 SEA ABB=ON  (ACID#(L)(MINERAL OR INORG?))/IT
L79        136703 SEA ABB=ON  (ACID#(2A)(MINERAL OR INORG?))
L80            33 SEA ABB=ON  L61 AND (L69 OR L70 OR L74 OR L75 OR L76 OR L77 OR
                  L78 OR L79)
L81             6 SEA ABB=ON  L61 AND (L69 OR L70) AND (L74 OR L75 OR L76 OR L77
                  OR L78 OR L79)
L82             6 SEA ABB=ON  L61 AND (((L74 OR L75) AND (L76 OR L77 OR L78 OR
                  L79)) OR ((L76 OR L77) AND (L78 OR L79)))

     INDEX '1MOBILITY, 2MOBILITY, ABI-INFORM, ADISCTI, AEROSPACE, AGRICOLA,
     ALUMINIUM, ANABSTR, ANTE, APOLLIT, AQUALINE, AQUASCI, AQUIRE, BABS,
     BIBLIODATA, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA,
     CAOLD, CAPLUS, CASREACT, CBNB, CEABA-VTB, CERAB, ...' ENTERED AT 10:07:46
     ON 29 MAR 2007
               SEA (RIBOFLAVIN OR VITAMIN B2) AND (MODIF?(2A)(B OR C OR BC))
              ---------
              1   FILE AEROSPACE
              1   FILE AGRICOLA
              1   FILE BIOENG
              3   FILE BIOSIS
              1   FILE BIOTECHABS
              1   FILE BIOTECHDS
              1   FILE BIOTECHNO
              2   FILE CABA
              6   FILE CAPLUS
              3   FILE CEABA-VTB
              1   FILE COMPENDEX
              1   FILE DDFB
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                2   FILE DPCI
                1   FILE DRUGB
                2   FILE EMBASE
                1   FILE ENERGY
              113   FILE EPFULL
                2   FILE ESBIOBASE
                1   FILE FRFULL
                2   FILE FROSTI
                3   FILE FSTA
                7   FILE GBFULL
              394   FILE GENBANK
                4   FILE IFIPAT
               11   FILE INPADOC
                1   FILE LIFESCI
                1   FILE MEDLINE
                2   FILE NLDB
                1   FILE PASCAL
                3   FILE PATDPA
              111   FILE PATDPAFULL
              590   FILE PCTFULL
                1   FILE PROMT
                1   FILE RDISCLOSURE
                6   FILE SCISEARCH
                2   FILE TOXCENTER
             1176   FILE USPATFULL
               89   FILE USPAT2
                6   FILE WPIDS
                1   FILE WPIFV
                6   FILE WPINDEX
L83              QUE ABB=ON  (RIBOFLAVIN OR VITAMIN B2) AND (MODIF?(2A)(B OR C
                 OR BC))
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     FILE 'STNGUIDE' ENTERED AT 10:13:02 ON 29 MAR 2007

     FILE 'MEDLINE, DRUGB, AGRICOLA, PASCAL, FROSTI, CABA, BIOTECHNO, BIOSIS,
     BIOTECHDS, ESBIOBASE, LIFESCI, FSTA, TOXCENTER, BIOENG, CEABA-VTB,
     EMBASE, DPCI, SCISEARCH' ENTERED AT 10:19:09 ON 29 MAR 2007
L84          1515 SEA ABB=ON  FRANKE D?/AU
L85          3683 SEA ABB=ON  HILL F?/AU
L86         32495 SEA ABB=ON  MARTIN C?/AU
L87            22 SEA ABB=ON  KNEBEL T?/AU
L88         26733 SEA ABB=ON  L2
L89         51821 SEA ABB=ON  RIBOFLAVIN OR RIBO FLAVIN OR VITAMIN B2 OR
                  VITAMINB2
L90         33382 SEA ABB=ON  MODIF?(2A)(B OR C OR BC)
L91         77692 SEA ABB=ON  FLUIDI?(W) BED#
L92        674348 SEA ABB=ON  PRECIPITAT?
L93         25900 SEA ABB=ON  (ACID#(2A)(MINERAL OR INORG?))
L94       1406599 SEA ABB=ON  GRANUL?
L95             5 SEA ABB=ON  (L84 AND L85 AND L86 AND L87) OR ((L84 OR L85 OR
                  L86 OR L87) AND (L88 OR L89) AND (L90 OR L91 OR L92 OR L93 OR
                  L94))
L96            11 SEA ABB=ON  L88 AND L90
L97            35 SEA ABB=ON  L89 AND L90
L98             5 SEA ABB=ON  L97 AND L94
L99             1 SEA ABB=ON  L97 AND ((L91 AND (L92 OR L93)) OR (L92 AND L93))

L100            3 SEA ABB=ON  L97 AND (L91 OR L92 OR L93)
L101            6 SEA ABB=ON  L97 AND (PREP? OR MANUF?)
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     FILE 'STNGUIDE' ENTERED AT 10:26:57 ON 29 MAR 2007

     FILE 'MEDLINE, DRUGB, AGRICOLA, PASCAL, FROSTI, CABA, BIOTECHNO, BIOSIS,
     BIOTECHDS, ESBIOBASE, LIFESCI, FSTA, TOXCENTER, BIOENG, CEABA-VTB,
     EMBASE, DPCI, SCISEARCH' ENTERED AT 10:28:26 ON 29 MAR 2007
               D QUE L95

     FILE 'WPIX' ENTERED AT 10:28:29 ON 29 MAR 2007
               D QUE L43

     FILE 'USPATFULL' ENTERED AT 10:28:31 ON 29 MAR 2007
               D QUE L71

     FILE 'CAPLUS' ENTERED AT 10:28:32 ON 29 MAR 2007
               D QUE L1
               D QUE L7
               D QUE L11
L102            3 SEA ABB=ON  (L1 OR L7 OR L11)

     FILE 'CAPLUS, LIFESCI, BIOENG, DPCI, WPIX, USPATFULL' ENTERED AT 10:28:34
     ON 29 MAR 2007
L103           15 DUP REM L102 L95 L43 L71 (1 DUPLICATE REMOVED)
                     ANSWERS '1-3' FROM FILE CAPLUS
                     ANSWER '4' FROM FILE LIFESCI
                     ANSWER '5' FROM FILE BIOENG
                     ANSWERS '6-8' FROM FILE DPCI
                     ANSWERS '9-11' FROM FILE WPIX
                     ANSWERS '12-15' FROM FILE USPATFULL
                D ABS IBIB HITSTR 1-3
                D IALL 4-8
                D IALL ABEQ TECH 9-11
                D IBIB ABS HITIND 12-15

     FILE 'STNGUIDE' ENTERED AT 10:30:26 ON 29 MAR 2007

     FILE 'MEDLINE, DRUGB, AGRICOLA, PASCAL, FROSTI, CABA, BIOTECHNO, BIOSIS,
     BIOTECHDS, ESBIOBASE, LIFESCI, FSTA, TOXCENTER, BIOENG, CEABA-VTB,
     EMBASE, DPCI, SCISEARCH' ENTERED AT 10:32:43 ON 29 MAR 2007
               D QUE L96
               D QUE L98
               D QUE L100
               D QUE L101
L104           18 SEA ABB=ON  (L96 OR L98 OR L100 OR L101)
L105           17 SEA ABB=ON  L104 NOT L95

     FILE 'WPIX' ENTERED AT 10:33:15 ON 29 MAR 2007
               D QUE L47
               D QUE L49
               D QUE L52
               D QUE L57
L106           10 SEA ABB=ON  (L47 OR L49 OR L52 OR L57) NOT L43

     FILE 'USPATFULL' ENTERED AT 10:33:21 ON 29 MAR 2007
               D QUE L72
               D QUE L73
               D QUE L81
               D QUE L82
L107           10 SEA ABB=ON  (L72 OR L73 OR L81 OR L82) NOT L71
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     FILE 'CAPLUS' ENTERED AT 10:33:25 ON 29 MAR 2007
                D QUE L14
                D QUE L23
                D QUE L24
                D QUE L25
                D QUE L26
L108           11 SEA ABB=ON  (L14 OR L23 OR L24 OR L25 OR L26) NOT L102

     FILE 'CAPLUS, MEDLINE, AGRICOLA, PASCAL, FROSTI, CABA, BIOTECHNO, BIOSIS,
     BIOTECHDS, ESBIOBASE, TOXCENTER, EMBASE, DPCI, WPIX, USPATFULL' ENTERED
     AT 10:33:41 ON 29 MAR 2007
L109           39 DUP REM L108 L105 L106 L107 (9 DUPLICATES REMOVED)
                     ANSWERS '1-11' FROM FILE CAPLUS
                     ANSWER '12' FROM FILE MEDLINE
                     ANSWER '13' FROM FILE PASCAL
                     ANSWER '14' FROM FILE FROSTI
                     ANSWERS '15-16' FROM FILE CABA
                     ANSWERS '17-19' FROM FILE BIOSIS
                     ANSWER '20' FROM FILE TOXCENTER
                     ANSWER '21' FROM FILE DPCI
                     ANSWERS '22-30' FROM FILE WPIX
                     ANSWERS '31-39' FROM FILE USPATFULL
                D ABS IBIB ED HITSTR 1-11
                D IALL 12-21
                D IALL ABEQ TECH 22-30
                D IBIB ABS HIT 31-39

     FILE 'HOME' ENTERED AT 10:35:27 ON 29 MAR 2007

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